Application of the stereoselective cycloaddition of sulfenic acids with alkenes in target synthesis chemistry

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Application of the stereoselective cycloaddition of sulfenic acids with alkenes in target synthesis

A thesis presented by

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To Pier Luigi e Francesca

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Abstract

Sulfenic acids are highly reactive species generated in the well-known and often utilised thermal elimination of sulfoxides to give alkenes. The reverse reaction, the addition of a sulfenic acid to an alkene, is also known, and is subject to the same geometric constraints in the transition state ie the need to achieve coplanarity for the 5 atoms participating in a concerted syn elimination/addition. Intramolecularly, this can lead to high levels of regio- and diastereocontrol, elegantly demonstrated by Jones in the 1970's for the diastereoselective formation of sulfur heterocycles (Chapter 1).

This methodology has been extended to a novel "group selective" sulfenic acid intramolecular cycloaddition reaction to produce *cis*-fused perhydrobenzothiophene-S-oxides. Thermolysis of a *t*-butyl sulfoxide gives rise to a sulfenic acid intermediate which in turn cyclises on to one of two prochiral alkenes to provide the corresponding cyclic sulfoxides. It is shown that the ratio of sulfoxides is influenced by the nature of the protecting group on an alcohol in the connecting chain. A number of protecting groups have been surveyed, with TBDMS providing the highest selectivity in the cyclisation. The selectivity of the cyclisation process with different functional groups at the ipso position (*t*-Bu, *i*-Pr, *i*-Bu) has been explored. The aim is to apply this methodology in the synthesis of breynolide, the aglycon hydrolysis product of breyins A and B, two novel sulfur-containing glycosides which show oral hypocholesterolemic activity (Chapter 2).

During the course of these studies an interesting synthesis of the 1,4-oxathiane ring system has been discovered. This methodology has been applied in the synthesis of potential antifungal agents (Chapter 3).

Finally, studies have been carried out towards the stereoselective synthesis of the highly oxygenated cyclohexane fragment present in several natural products, such as phyllaemblic acid, phyllantocin and breynolide itself (Chapter 4).

Contents

Abbreviations

Ac	acetyl
Ar	aryl
BMEA	bis(methoxyethyl)amine
Bn	benzyl
bp	boiling point
BPS	*t*-butylbiphenylsilyl
Bu	butyl
Bz	benzoyl
i-Bu	*iso*-butyl
n-Bu	*normal*-butyl
s-Bu	*secondary*-butyl
t-Bu	*tert*-butyl
°C	degrees centigrade
CBz	carboxybenzyl
CI	chemical ionisation
m-CPBA	*meta*-chloroperbenzoic acid
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DBB	4,4'-di-*t*-butylbiphenyl
DCM	dichloromethane
de	diastereoisomeric excess

DIBAL-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
2,2-DMP	2,2-dimethoxypropane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EI	electronic ionisation
Et	ethyl
FAB	fast atom bombardment
h	hour
HMPA	hexamethylphosphoramide
IR	infra-red
LDA	lithium diisopropylamide
M	molar
Me	methyl
MEM	2-methoxyethoxymethyl
min	minute
mp	melting point
m-MPM	*meta*-methoxyphenylmethyl
MSH	*O*-mesitylenesulfonylhydroxylamine
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
Ph	phenyl

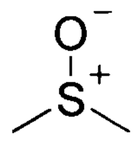
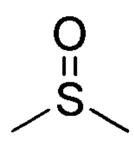
i-Pr	*iso*-propyl
Pr	propyl
rt	room temperature
SEM	2-(trimethylsilyl)ethoxymethyl
t	tertiary
TBAF	tetrabutylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
Tf	trifluoromethanesulfonate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TMSI	trimethylsulfoxonium iodide
TRITON B	*N*-benzyltrimethyl ammonium hydroxide
TsOH	*para*-toluene sulfonic acid
v/*v*	volume for volume
w/*v*	weight for volume

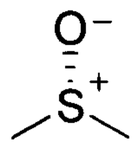
Nuclear Magnetic Resonance

Ar-H	aromatic proton
Ar-C	aromatic carbon

br	broad
δ	chemical shift
d	doublet
dd	double doublet
H	hertz
J	coupling constant
m	multiplet
ppm	parts per million
q	quartet
s	singlet
t	triplet

Representation

sulfoxide  vs. 

chirality  denotes enantiomerically pure and racemic

Chapter 1

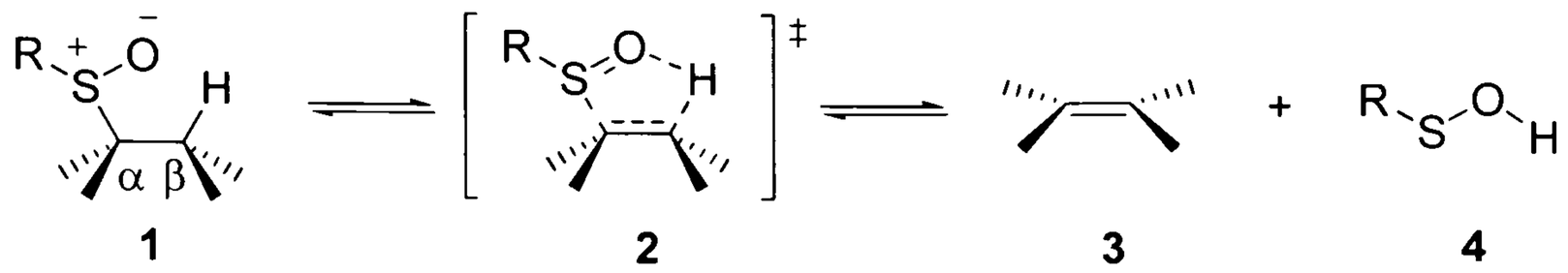
Section 1.1: General introduction - Chirality in synthesis

Organic compounds play an important role in modern life in materials which possess biological activity. The biological activity is expressed by the interaction of such organic compounds with bio-molecules such as enzymes or nucleic acids. These sites of interaction are constructed by chiral building blocks such as amino acids or carbohydrates, so the bio-molecules are chiral themselves. If the organic compound is chiral itself, the biological response of the interaction of the two chiral systems can depend on the stereochemistry of both systems. The enantiomers of any biological active compound would interact differently with the natural molecule. The enantiomers would probably possess different biological activity, and can be considered as different compounds. The use of a racemic mixture of an active biological compound is equal to the use of two different compounds. The most controversial example of this was the 1960's manufacture of a sedative and anti-nausea drug called Thalidomide, which was prepared as a racemic mixture. The compound was said to be ideal for tackling morning sickness in pregnant women but was found to cause defects in new born babies. While the (*R*)-enantiomer was the active sedative, the (*S*)-enantiomer was later found to cause the defects.

The obvious solution to the use of a racemate is to use only the enantiomer which possesses the desired biological activity, and this solution relies on the single enantiomer to be available. Two possible methods can be employed: resolution of the racemate and the use of an enantiomerically pure starting material.[1] A general solution to the problem of obtaining enantiomerically pure organic compounds would be to have synthetic methods which result in the desired transformation and control the absolute stereochemistry of chiral centres which are created as a result of the synthetic operation. This is the area of asymmetric synthesis.

Section 1.2: Sulfenic acid chemistry

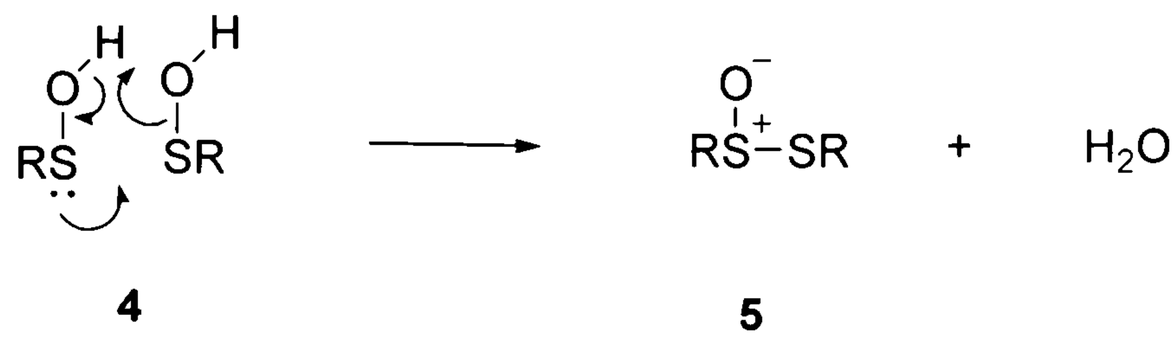
The synthesis and application of organosulfur compounds plays an important role in organic synthesis. One of the most useful synthetic applications of organosulfur compounds is the thermal elimination of sulfoxides to give alkenes.[2] A number of investigations have shown that sulfoxides with one or more hydrogens on a ß-carbon adjacent to the sulfur atom undergo facile decomposition at moderate temperatures to give alkenes **3** and sulfenic acids **4** (Scheme 1).



Scheme 1

The thermal elimination of sulfoxides was first reported by Kingsbury and Cram in 1960.[3] The reversible mechanism they proposed involves a stereospecific *syn*-elimination within a 5-membered ring transition state **2** in which all 5 participating atoms achieve coplanarity. In the pericyclic rearrangement (E_i reaction), the leaving group abstracts a hydrogen from the ß-carbon in what may be perceived as an intramolecular acid-base reaction. Theoretical studies have demonstrated the validity of the concerted mechanism for the *syn*-elimination of sulfoxides.[4] The "concertedness" of the elimination does not imply the *synchronicity* of events. In the elimination reaction the breakage of the 'C-S' bond occurs prior to that of the corresponding 'C-H' bond. In other words, the transition state for the E_i elimination is approximately symmetrical with respect to bond formation and dissociation.

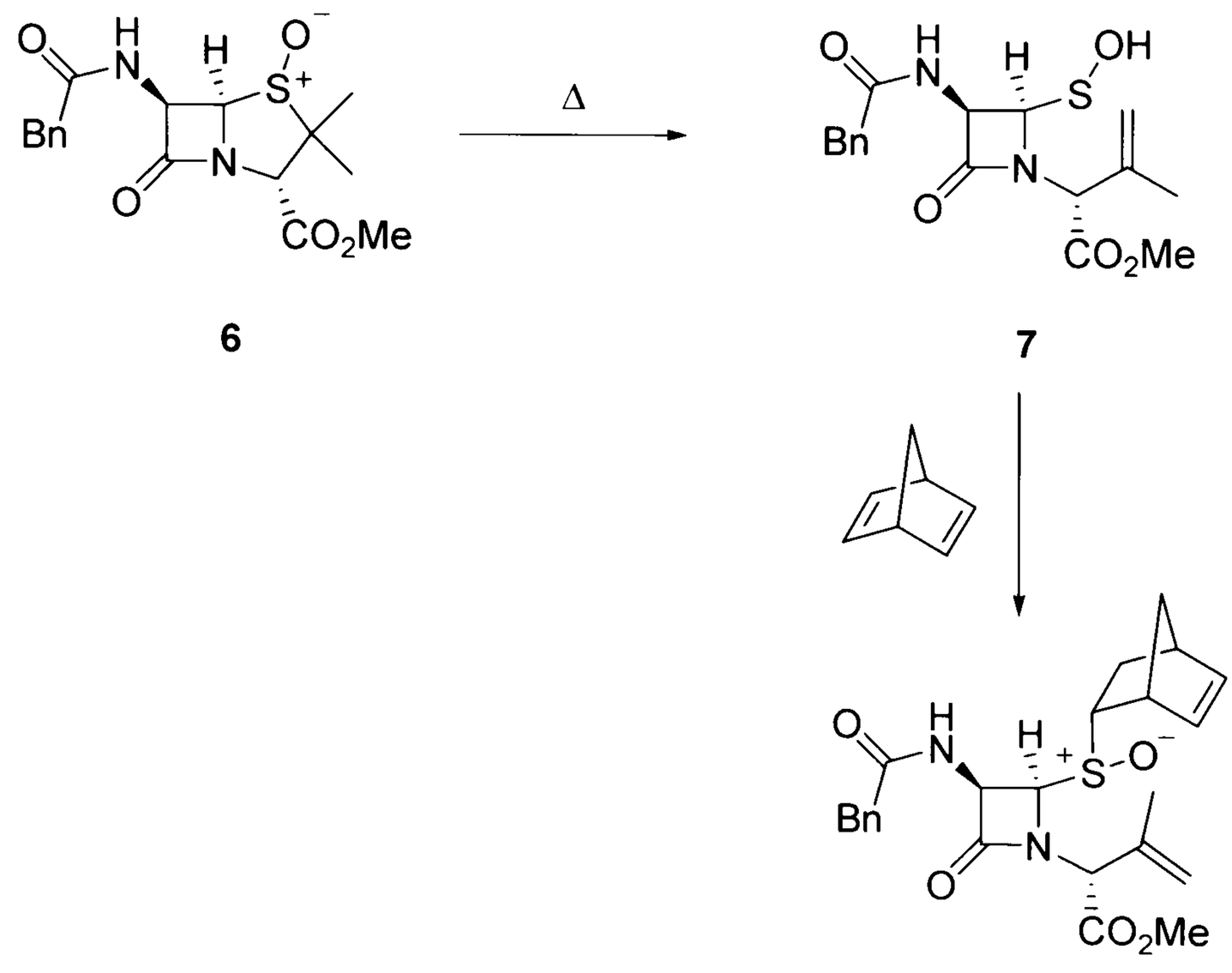
Sulfenic acids **4** are a further byproduct of this reaction but they are usually too unstable to be isolated as they readily undergo intermolecular dehydration to give thiosulfinates **5** as depicted in Scheme 2.[5]



4 **5**

Scheme 2

A trapping agent is often utilised to prove the existence of unstable sulfenic acid species.[6,7] As an example, the thermal elimination of the penicillin sulfoxide **6** afforded the unstable sulfenic acid intermediate **7**, which was subsequently trapped with norbornadiene to give the resulting sulfoxide **8** (Scheme 3).[8]

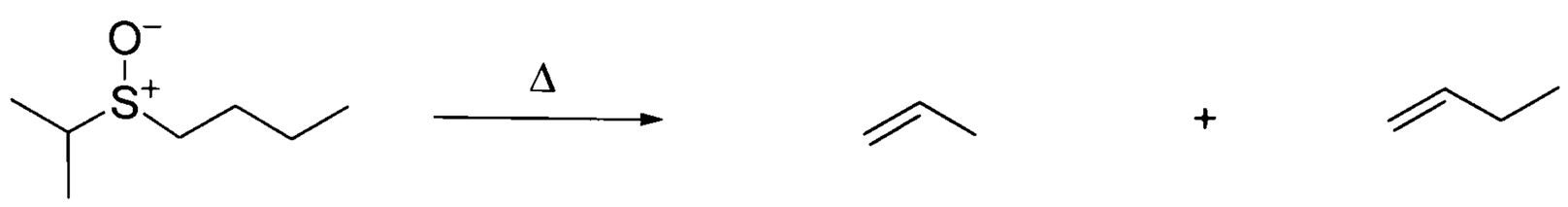


6 **7** **8**

Scheme 3

Following Cram's initial report,[3] further research has been conducted to analyse the precise factors which influence the elimination. For example, Emerson and co-workers have shown that it is not only statistical factors that control the regioselectivity of the thermolysis of sulfoxide.[9] In fact in unsymmetrical dialkyl sulfoxides there is an

enhanced tendency of thermolytic cleavage of the bond connecting sulfur to the more highly substituted alkyl group (Scheme 4). Pyrolysis of *n*-butyl isopropyl sulfoxide **9** affords propene **10** and 1-butene **11**. The yield of propene **10** (88%) derived from the secondary alkyl group exceeds the amount (75%) to be expected on the basis of the relative numbers of β-hydrogens in the two alkyl groups.

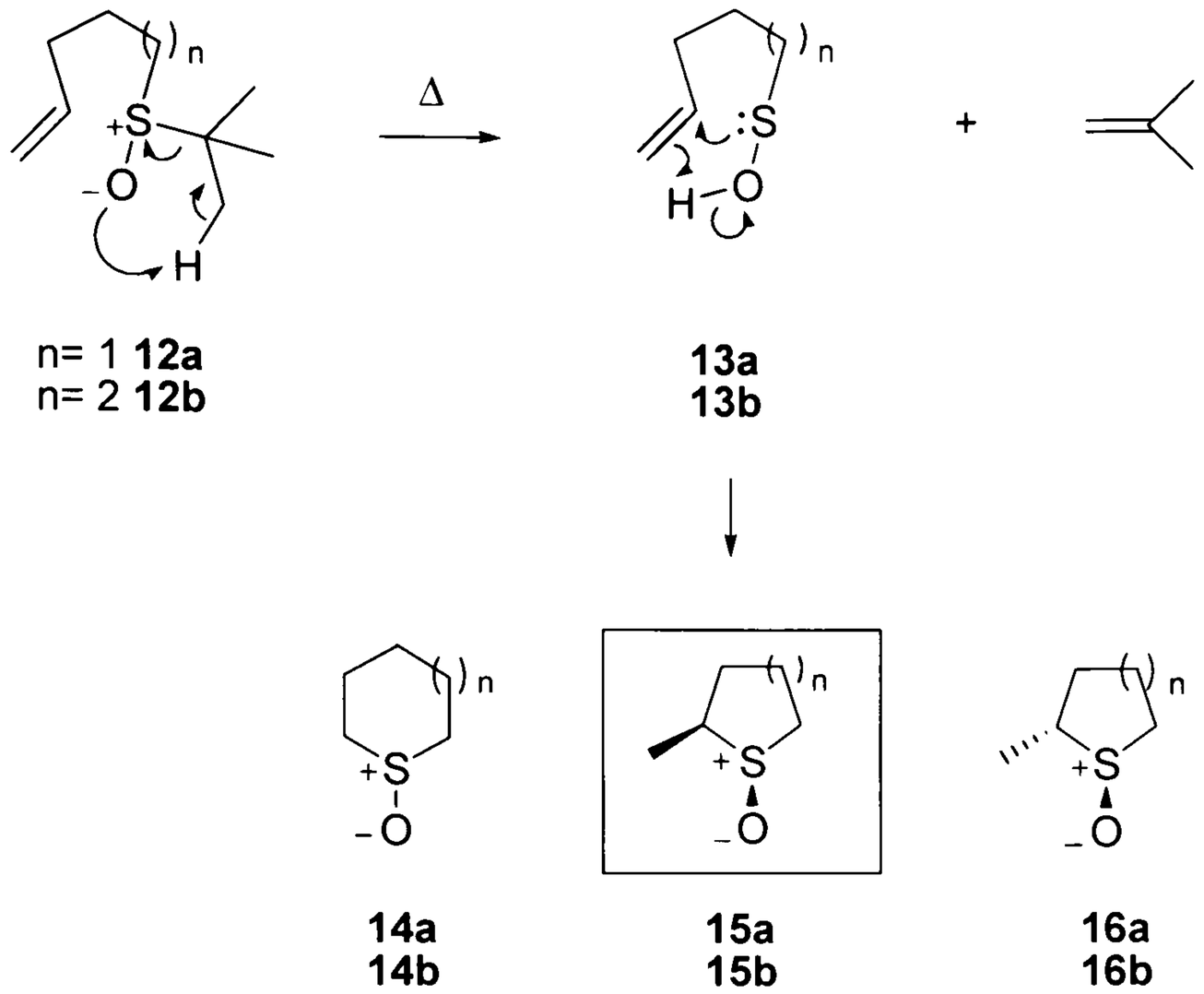


9 **10** **11**

88%, experimental result
75%, statistical ratio

Scheme 4

The alkene is frequently the desired product of the thermally induced elimination of sulfoxides. The reverse reaction, the addition of a sulfenic acid to an alkene to form a sulfoxide, is relatively under exploited in comparison, but has found some applications in synthesis and is subject to the same concerted *syn*-intramolecular mechanism. Jones and co-workers exploited the reversibility of this reaction in an elegant tandem sulfoxide elimination-*intra*molecular sulfenic acid addition to form cyclic sulfoxides with high levels of regio- and diastereocontrol.[10] They investigated the thermolysis of 5-*t*-butyl sulfinylpent-1-ene **12a** and **12b** (Scheme 5).



Scheme 5

The *t*-butyl sulfoxides **12a** and **12b** were chosen because they provided nine β-hydrogen atoms for the elimination, to maximise formation of the intermediate sulfenic acids **13a** and **13b**. For example, thermolysis of **12a** in xylene at 140 °C for 3 h gave *cis*-2-methyl-thiolan-1-oxide **15a** (74%) but none of the *trans*-diastereoisomer **16a** or thian-1-oxide **14a**. This result can be rationalised in terms of the geometrical requirements of the transition state for the concerted addition. Pent-5-ene-1-sulfenic acid **13a** can readily attain a cyclic array of the 5-participating atoms in the transition state **17** leading to *cis*-2-methyl-thiolan-1-oxide **15a** (Figure 1), whereas cyclic transition states are sterically impossible for the transformation required to give the *trans*-diastereoisomer **16a** or thian-1-oxide **14a**. Likewise **12b** afforded **15b** and none of **14b** and **16b**.

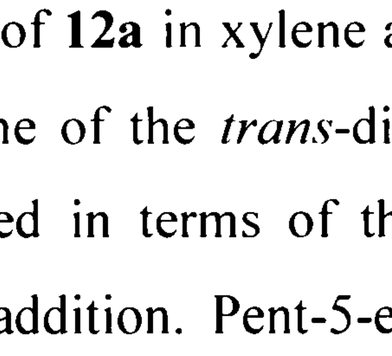
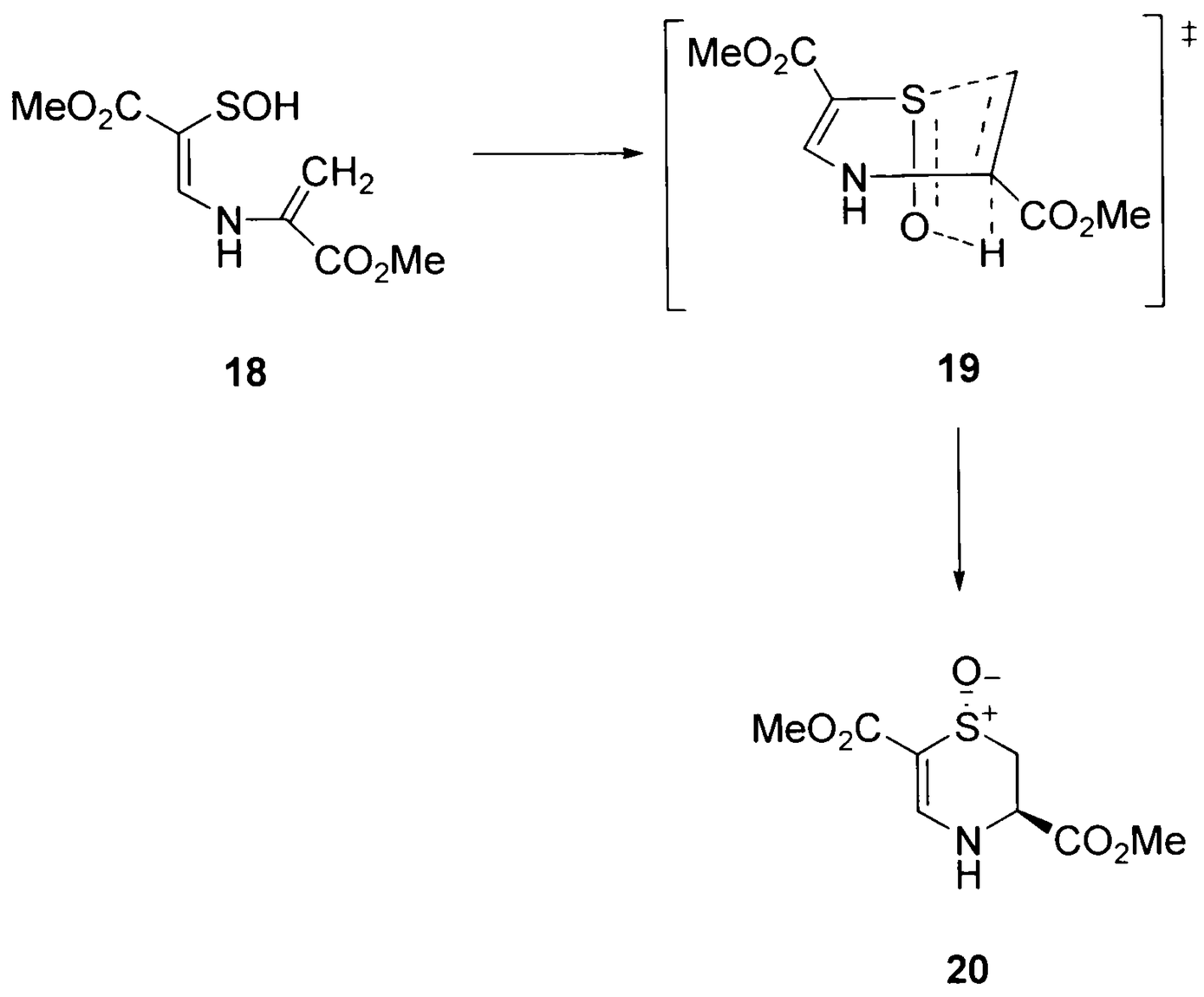


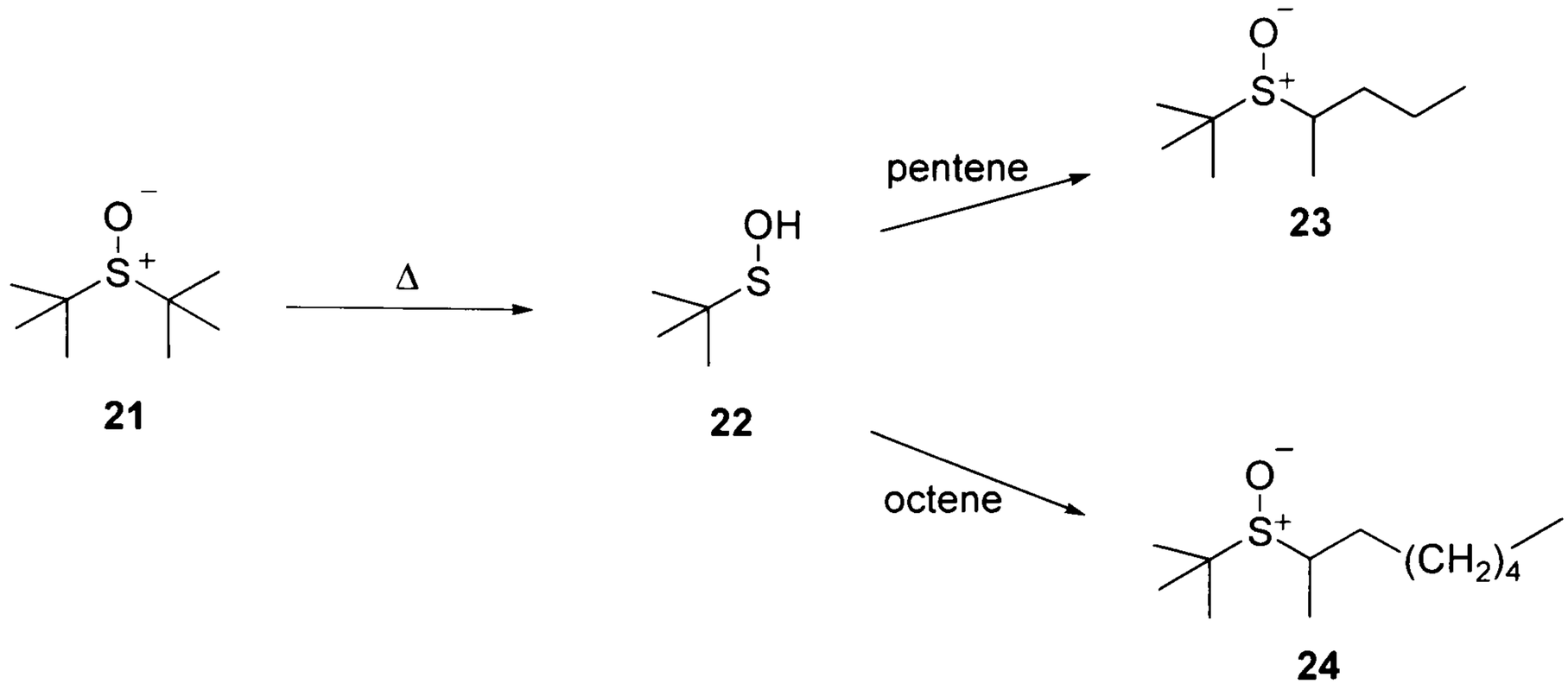
Figure 1

The ease of attainment of coplanarity of the five participating atoms influences the energy of the transition state. The tendency towards coplanarity in the cyclic transition state of elimination prior to the E_i mechanism is generally accepted. However, deviations from coplanarity can be more readily tolerated when the migrating hydrogen atom is rendered more acidic by an activating group, such as an ester functionality, as depicted in Scheme 6.[11] It is suggested that the transition state **19** is formed by a sigmatropic process, which demands that the sulfoxide possesses a *syn*-axial arrangement of the sulfinyl group and the tertiary hydrogen atom.



Scheme 6

For *inter*molecular reactions, sulfenic acids tend to add regioselectively to the more electrophilic carbon of the olefin in a Markovnikoff fashion.[9,12] For example, thermolysis of di-*t*-butyl sulfoxide **21** in pentene at 140 °C for 8 min and in boiling octene for 4 min gave 2-*t*-butyl sulfinylpentane **23** (83%) and 2-*t*-butyl sulfinyloctane **24** (74%) respectively (Scheme 7).[9]



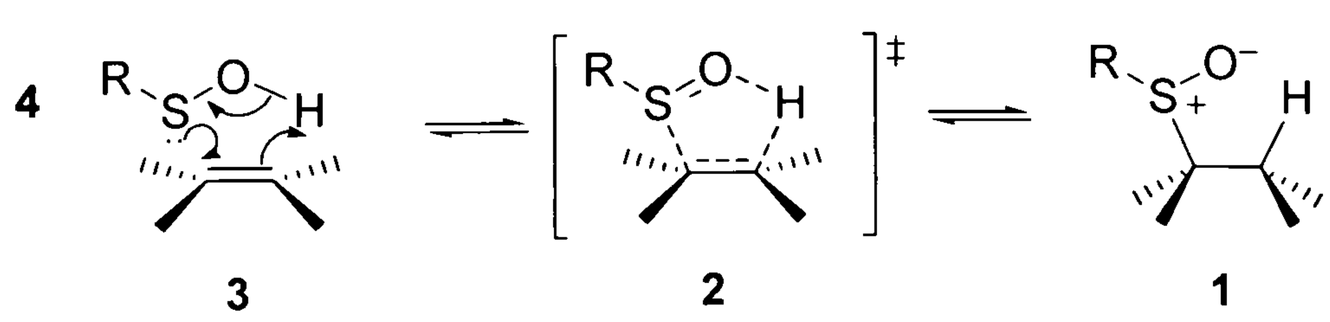
21 **22** **23** **24**

Scheme 7

These results are consistent with the thermal decomposition of di-*t*-butyl sulfoxide **21** to 2-methylpropane-2-sulfenic acid **22**, which in turn added in a regiospecific fashion to the olefin.

The regiospecifity of addition accords with the suggestion that the partial carbon-sulfur bond in the transition state for the reversible sigmatropic reaction is polarized in such a manner that the carbon atom has partial cationic character. Addition in a Markovnikoff manner should therefore be facilitated.

The reverse reaction, to reiterate, can be seen with the sulfur atom acting as the nucleophilic species whilst the sulfenic acid proton is removed by the π-bond acting as a Lewis base (in fact activated olefins have been used as trapping agents for sulfenic acids)[7,8] as shown in Scheme 8.

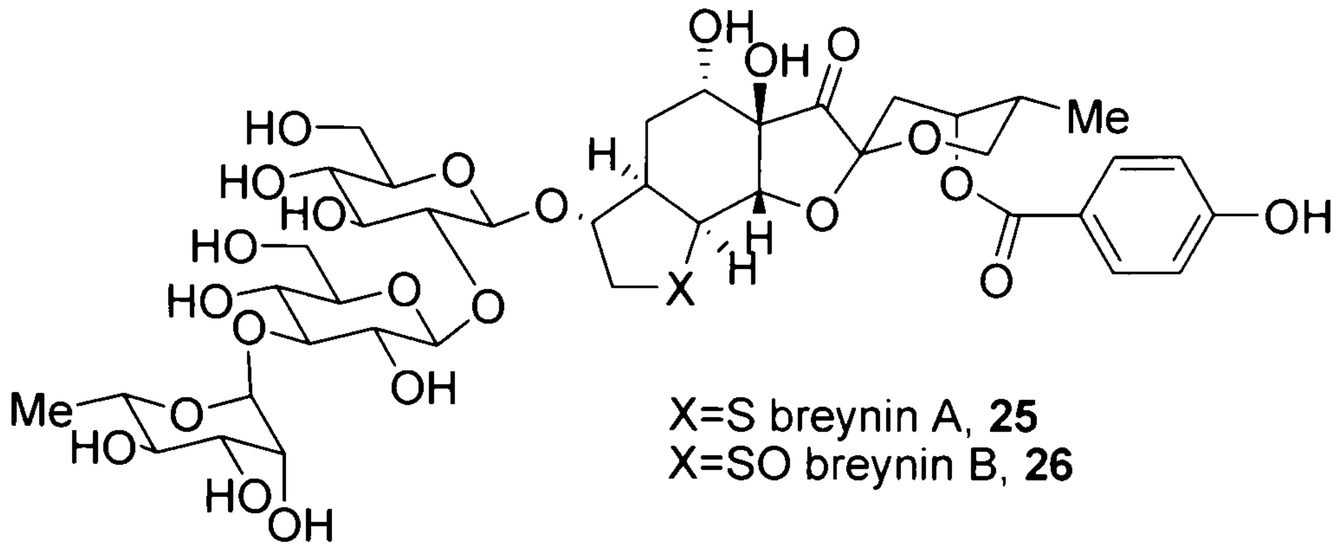


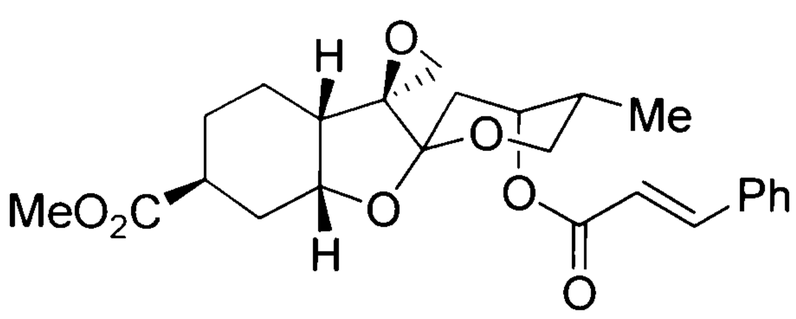
3 **2** **1**

Scheme 8

Section 1.3: Breynolide

Breynins A and B **25** and **26** are novel sulfur-containing glycosides which were isolated in the early 1970s from the Taiwanese woody shrub *Breynia officinalis* Hemsl, and have displayed significant oral hypocholesterolemic activity in rats (Figure 2).[13,14]





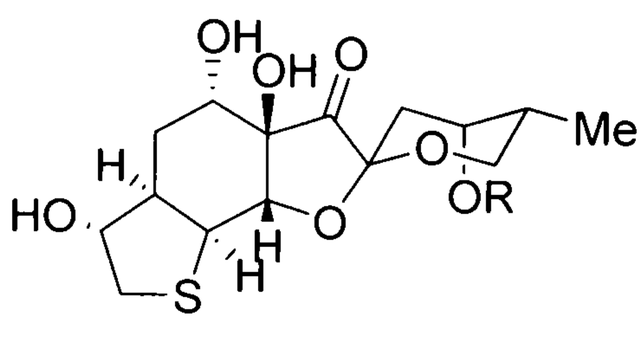
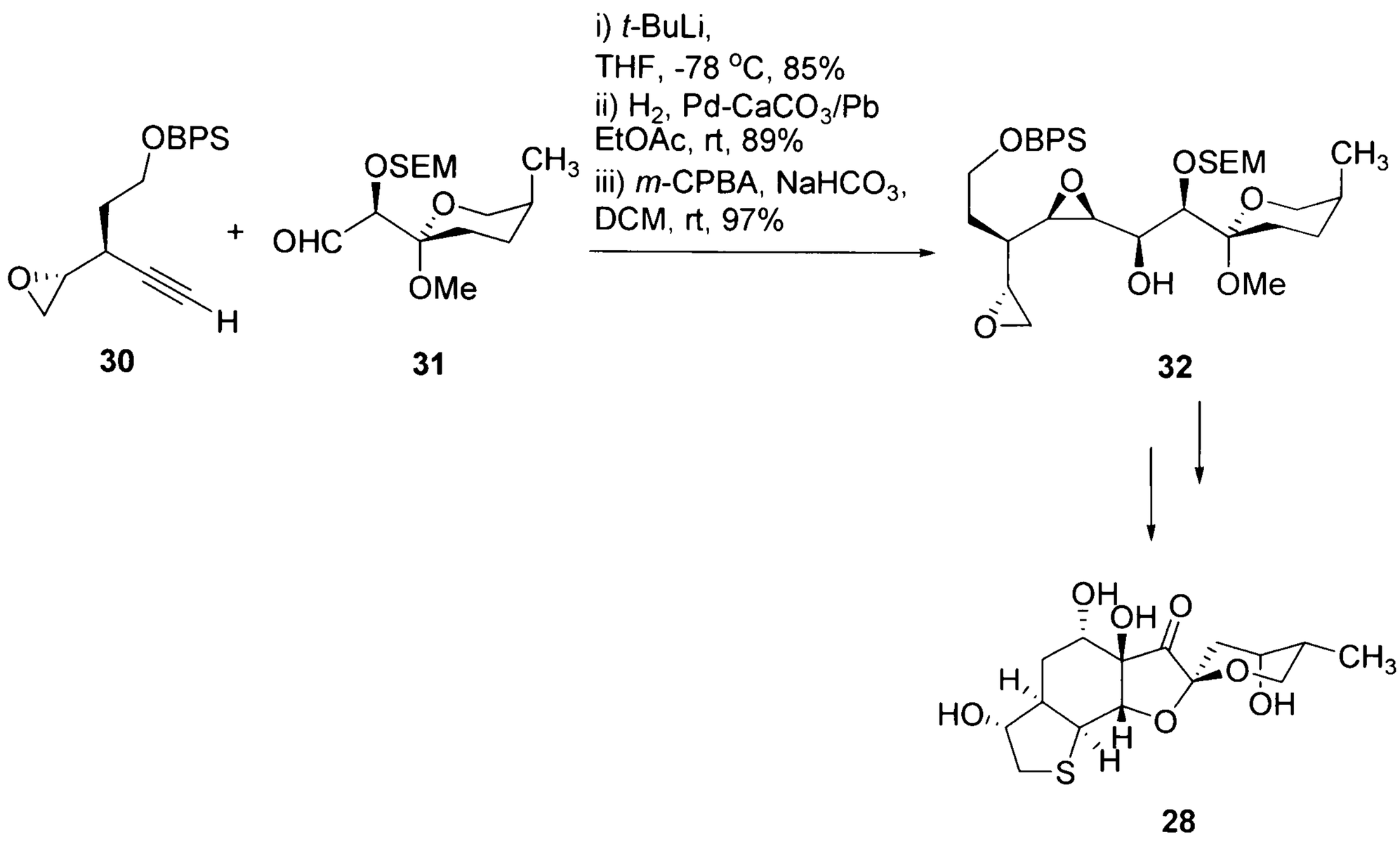


Figure 2

Researchers at the Bristol-Banyu Research Institute have characterized (+)-breynogenin **29** and (+)-breynolide **28** as the aglycon hydrolysis products of breynin A.[13] The relative and absolute stereochemistry of (+)-breynolide was unambiguously determined by Sasaki and Hirata through a single crystal X-ray structure analysis.[15] The interest in the breynins is justified by their pharmacological potential as well as their structural similarity to phyllanthocin **27**, the aglycon nucleus of the phyllanthostatin antitumor agents.[16] These incentives have stimulated several synthetic investigations,[17] with the first total synthesis of (+)-breynolide reported by Williams *et al* in 1990.[13]

There have been three total syntheses of breynolide **28** reported to date.[18] The first enantioselective total synthesis of (+)-breynolide was reported by Williams *et al* in 1990. This approach developed an efficient stereochemically convergent strategy for the synthesis of (+)-breynolide *via* the key intermediate **32**. The highly oxygenated intermediate **32** was synthesised coupling the two non-racemic chiral partners **30** and **31** as shown in Scheme 9.



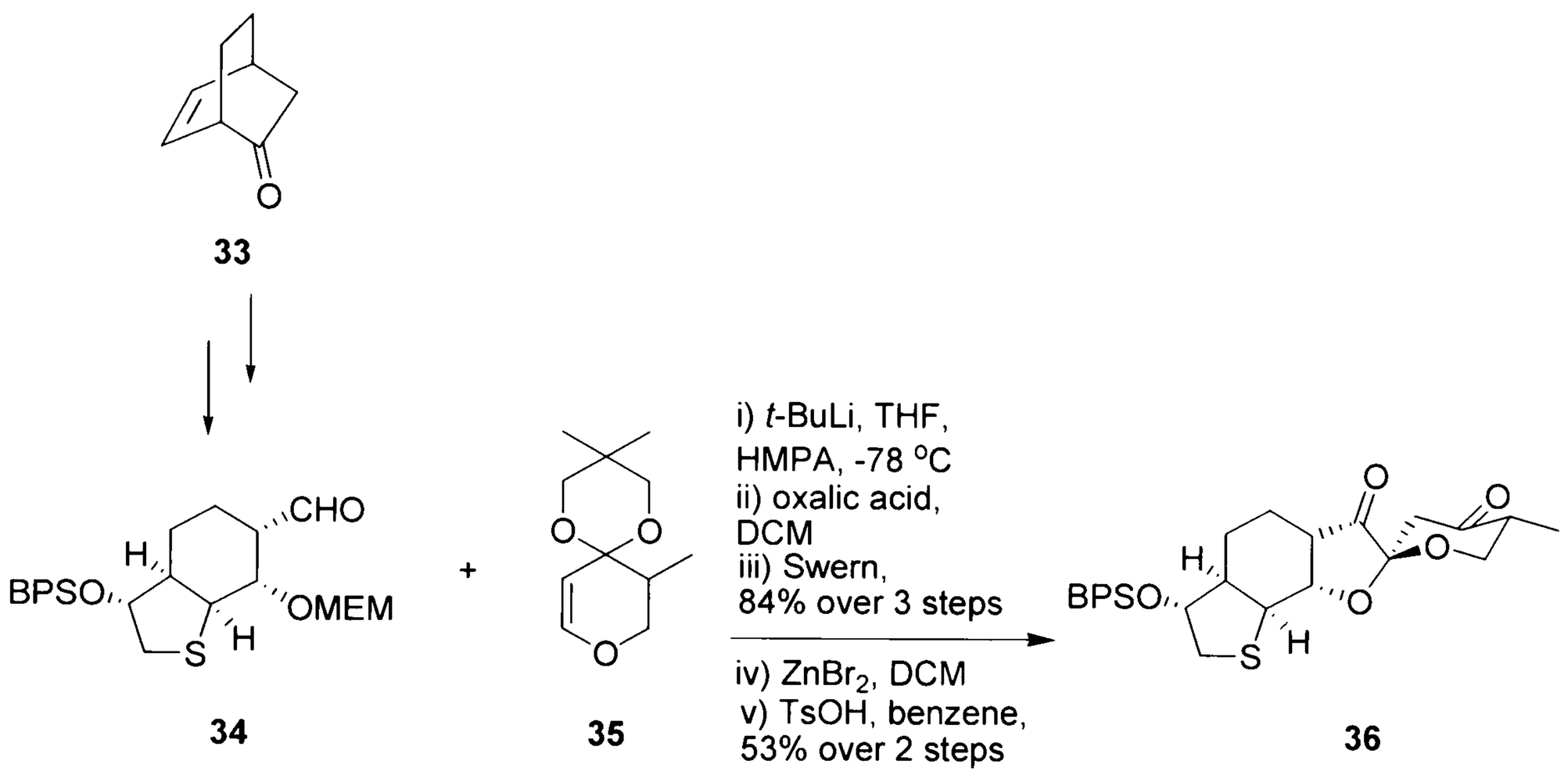
Scheme 9

Both coupling partners **30** and **31** are derived from asymmetric Sharpless epoxidations of allylic alcohols. The thioether functionality of breynolide **28** is set late in the synthesis, after oxygenation of the carbon framework.

The alternative strategies accomplished by Smith *et al*[14a] and by Burke and coworkers[17e] are based on stereochemically linear approaches, coupling a chiral species with a racemic mixture of enol ether **35**, the stereochemistry of which is unimportant as the methyl stereocentre can be controlled under equilibrating conditions later in the synthesis.

A `stereochemically linear` approach as the phrase suggests entails that a single stereochemical centre (or multiple centres generated in one transformation) introduced early in the synthetic sequence is used to induce the remaining relative stereocentres within the molecule (within breynolide, in this specific case).

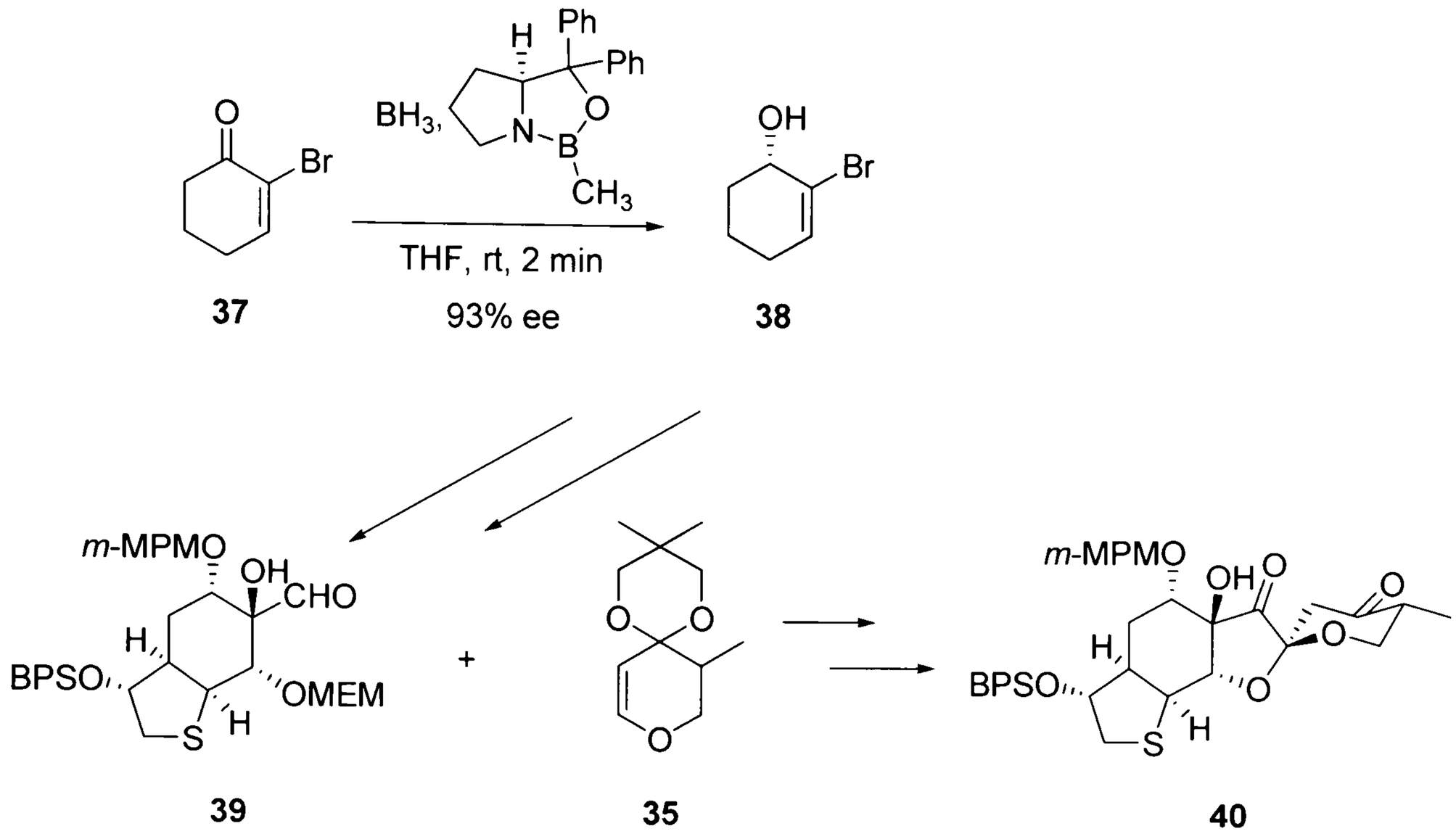
In Smith`s approach, the first stereocentre that enables all the others to be set is incorporated *via* a Diels-Alder reaction leading to **33**, in which the bridgehead α-carbon to the carbonyl becomes the α-carbon to the aldehyde in **34** (Scheme 10).



Scheme 10

Coupling of the racemic partner **35** with racemic aldehyde **34** and further functional group manipulation and spiroketalization afforded **36**, with the entire carbon framework of breynolide in hand. The spiroketalization manoeuver was effectuated under thermodynamic equilibration to obtain a single diastereoisomer **36**, albeit in racemic form. For the completion of the synthesis, selective reduction of the pyranone, insertion of the *trans* diol unit and deprotection was then accomplished.[14a]

Burke and coworkers utilised a similar approach, but coupled racemic **35** with the non-racemic chiral aldehyde **39** to achieve the total synthesis of (+)-breynolide, as depicted in Scheme 11.[17e]



Scheme 11

The first stereocentre introduced in **39** is the carbon connected to the *meta*-methoxyphenylmethyl ether, which is set by asymmetric CBS-reduction of the keto functionality of 2-bromo-2-cyclohexanone **37**. The six contiguous stereocentres in **39** are set by stereoselective manipulations of **38** under substrate control. The thioether is linked after all the oxygen functionalities are in place. The spiroketal **40** was then converted to (+)-breynolide, *via* selective reduction of the pyranone and deprotection.

Both stereochemically linear and convergent strategies have proven to be successful in elegant approaches to the total synthesis of breynolide.

The aim of this project was to investigate a new approach to the synthesis of breynolide **28** based upon the rapid assembly of a chiral perhydrobenzothiophene fragment, in which the thiolane ring is installed through a novel group selective cycloaddition reaction of an

alkene to a sulfenic acid. The process also delivers a sulfoxide moiety in a stereoselective manner, which may ultimately lead to the assignment of this stereocentre in breynin B **26**. This novel approach to breynolide differs from those previously reported in the early introduction of the sulfur atom into a building block which can be further elaborated chemo- and stereoselectively, and in the use of a sulfoxide group to control up to 5-stereogenic centres in the molecule.

Section 1.4: Group selective reactions in synthesis

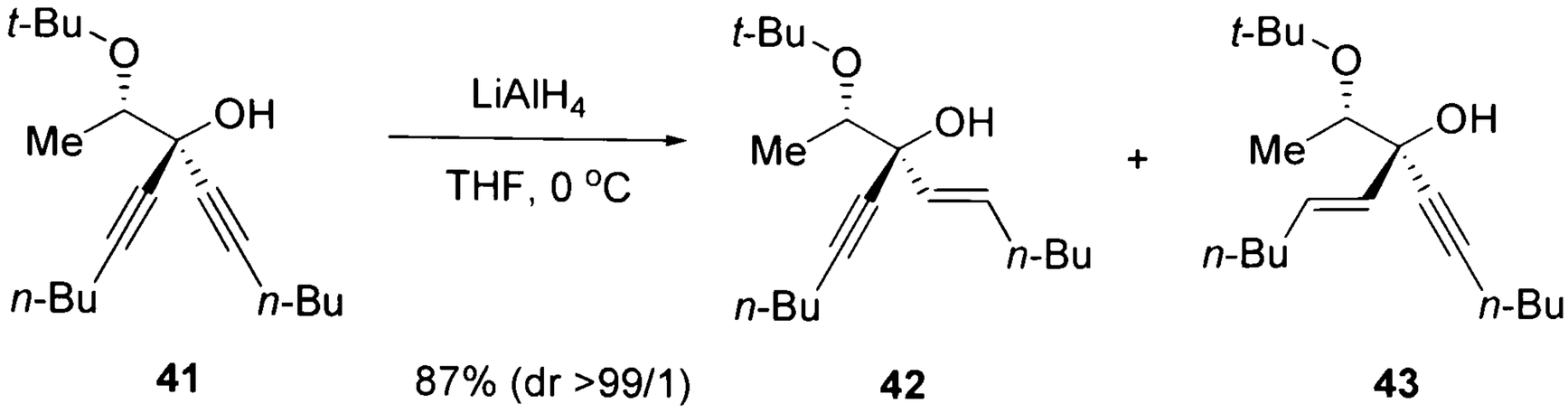
In asymmetric synthesis, employment of a group selective reaction can be a powerful strategy for the generation of stereocentres. In nature such group selective reactions are common and nowadays enzymatic methods have found widespread application in the area of enantioselective synthesis.[19]

It is possible to differentiate between diastereo- and enantiotopic groups according to symmetry criteria.[20] Groups within a molecule than can be transformed into each other by internal C_n-symmetry operations (n=2 usually, sometimes 3) are called homotopic. A molecule that possesses a C_n-axis of symmetry as the only symmetry element is chiral. Equal groups that do not fulfil the criteria for homotopy are named heterotopic. Heterotopic ligands can be further subdivided into enantiotopic and diastereotopic groups. If a molecule possesses as its only symmetry element a mirror plane, then the groups at the left and at the right of the mirror are enantiotopic. On the other hand, identical ligands that are non-superimposable on each other by symmetry operations, are classified as diastereotopic. Diastereotopic groups can exist also in achiral molecules.

The different chemical environment of diastereotopic groups allows for their differentiation. An important class of diastereoselective transformations involves the differentiation of diastereotopic groups through the influence of a pre-existing stereocentre covalently attached to the substrate. Functional groups that are known to be differentiated include hydroxyl-, ester-, carboxylic-, and olefinic groups. Iodolactonisation,[21] radical cyclisation,[22] spiro lactonisation and acetalisation,[23] Diels-Alder reaction,[24] intramolecular [3+2] and [2+2+1] cycloaddition,[25] intramolecular[26] and intermolecular[27] Michael addition, and intramolecular bis-silylation[28] have been reported as notable examples of diastereotopic group selective reactions with high level of stereocontrol. A few selected examples are presented to highlight the above argument.

In 2001 Suzuki and coworkers reported a new diastereotopic group-selective reaction which provided access to a class of stereo-defined *tert*-alcohols.[29] Stereogenic tertiary alcohols are embedded in many biologically active natural products. The group selective

hydroalumination of bis-alkynyl alcohols armed with an adjacent chiral centre stopped at the *mono*-hydroalumination stage, where one of the two 1-hexynyl groups had reacted predominantly (Scheme 12).



Scheme 12

The group selection could be attributed to the steric interactions of the substituents in the five-membered lithium chelate (Figure 3).

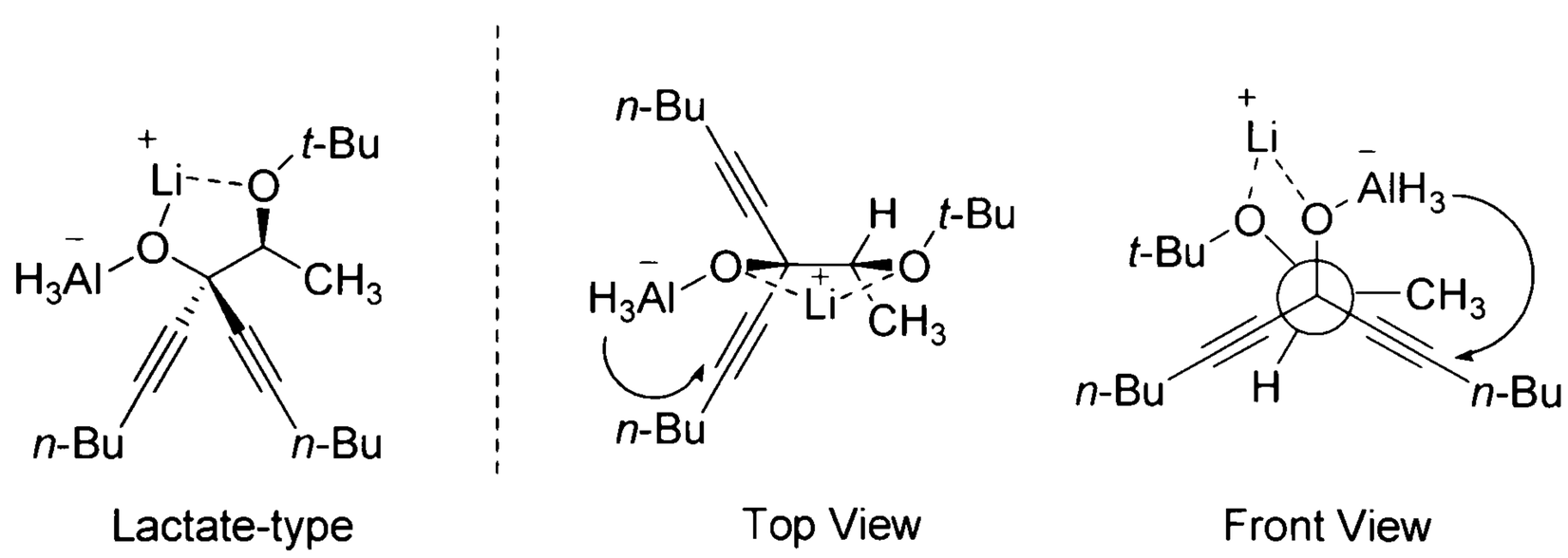
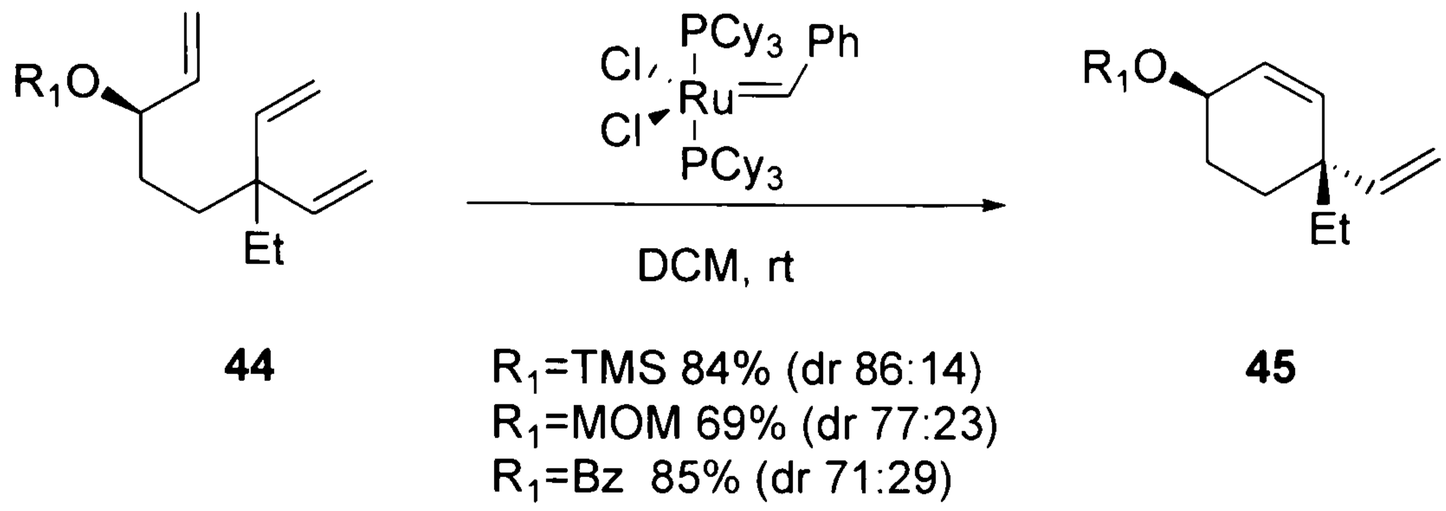


Figure 3

The alkynyl group closest to the aluminate is selective for hydroalumination. The steric encumberance of the α-alkoxy protecting group is necessary for achieving high selectivity. Recent work by the same group has extended the scope of the group selective hydroalumination reaction.[30]

Shishido *et al* have reported a methodology for the diastereoselective construction of a quaternary carbon stereocentre on a prochiral carbon *via* 1,4-asymmetric induction employing ring-closing metathesis.[31] The cyclohexene derivatives generated by this reaction are versatile and flexible chiral building blocks for the synthesis of biologically

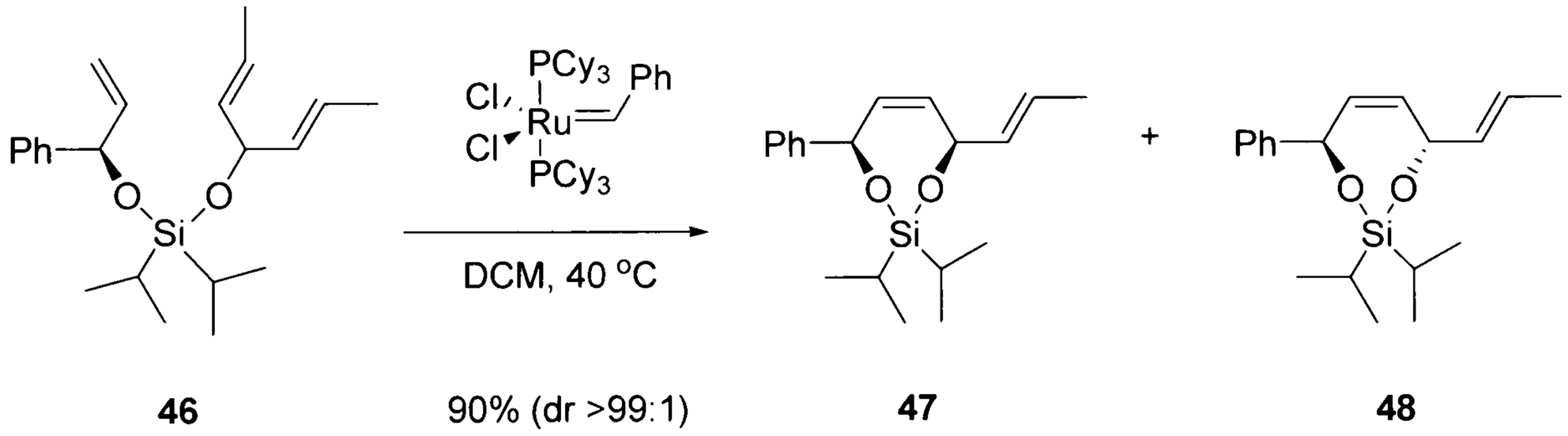
significant natural products. The triene substrate **44** underwent ring closing metathesis to afford diastereoenriched products dependent upon the R_1 substituent (Scheme 13).



44 R_1=TMS 84% (dr 86:14) R_1=MOM 69% (dr 77:23) R_1=Bz 85% (dr 71:29) **45**

Scheme 13

Evans and coworkers have used mixed bisalkoxy silanes in the ring-closing metathesis to achieve long-range asymmetric induction and provide an elegant construction of *cis*-1,4-silaketals (Scheme 14).[32]



46 90% (dr >99:1) **47** **48**

Scheme 14

The favoured transition state for the "temporary silicon-tethered RCM", gives rise to the preferential formation of the *cis*-1,4-silaketal (Figure 4).

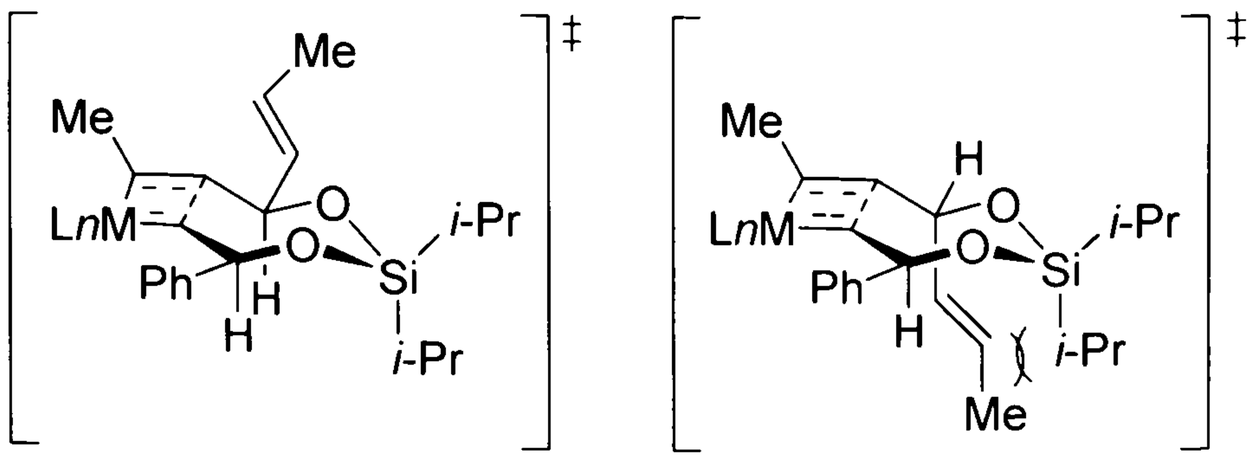


Figure 4

The *iso*-propyl group on silicon results in steric interactions with the pseudoaxial propenyl group in the disfavoured transition state.

When higher homologues are employed the opposite sense of diastereoinduction was observed, in favour of the *trans* product. The origin of the diastereoselectivity is consistent with the previous model, albeit with the pseudoaxial/equatorial positions reversed in the medium rings (Figure 5).

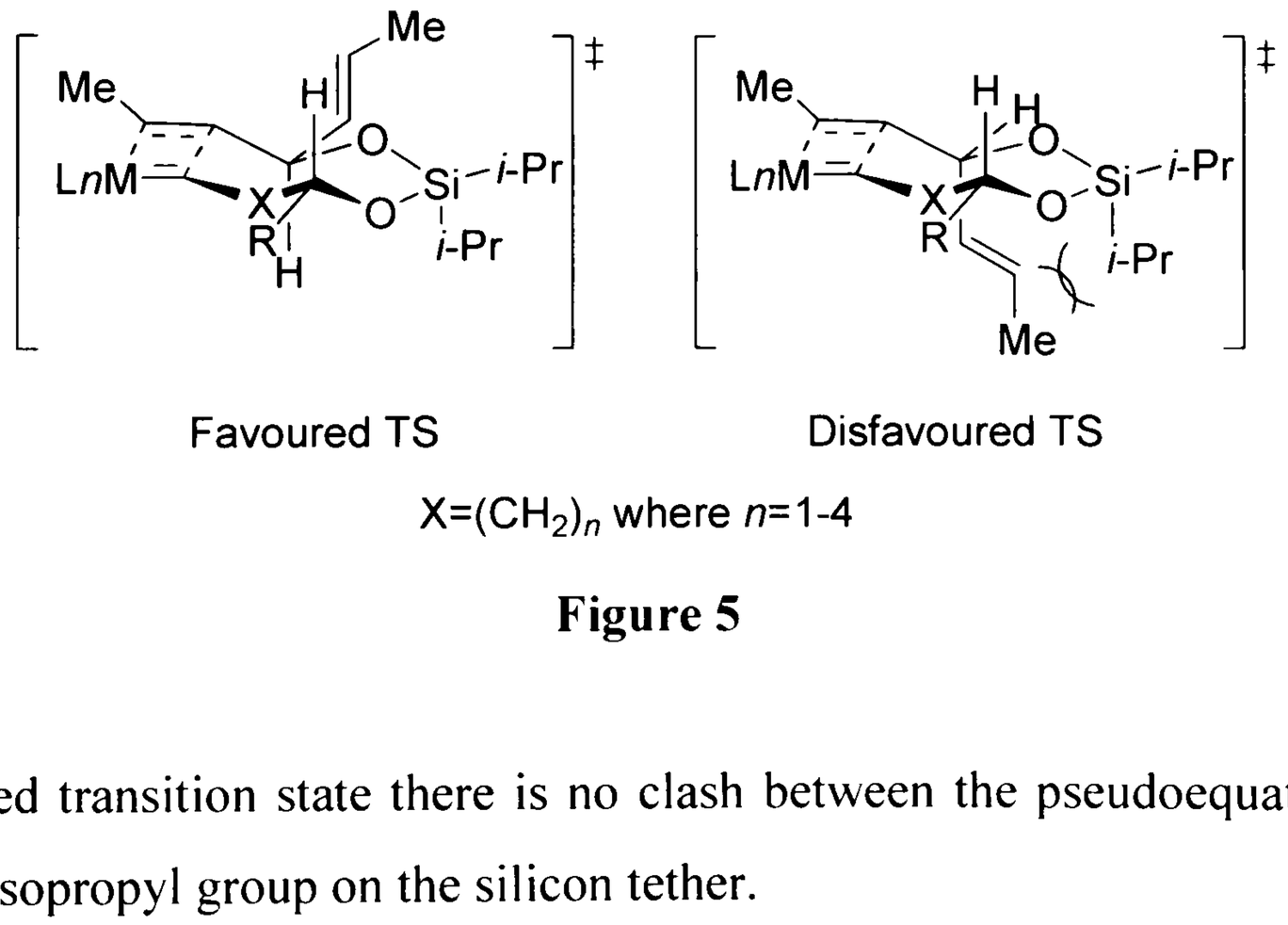
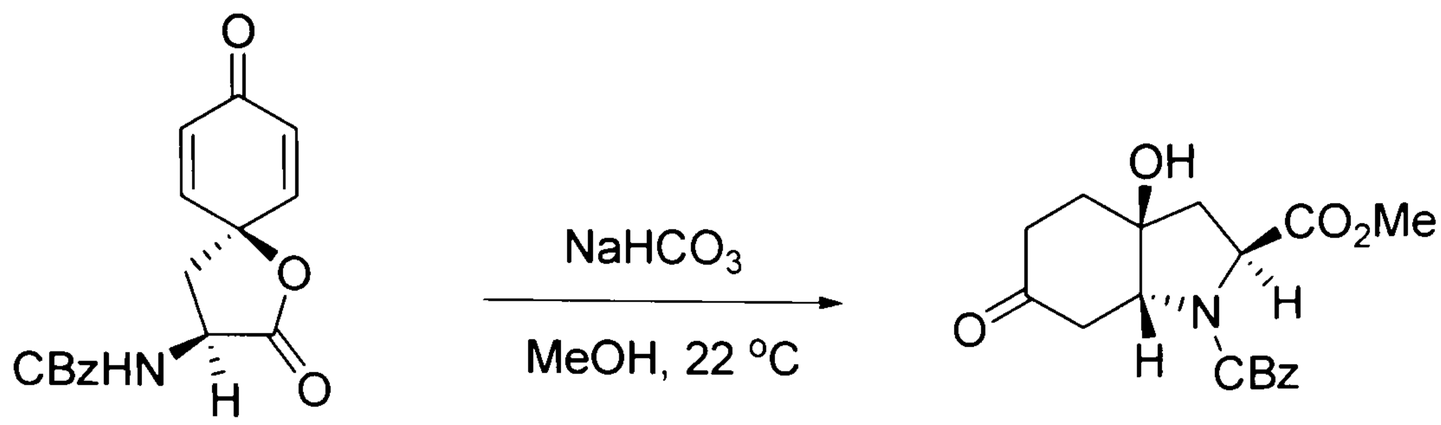


Figure 5

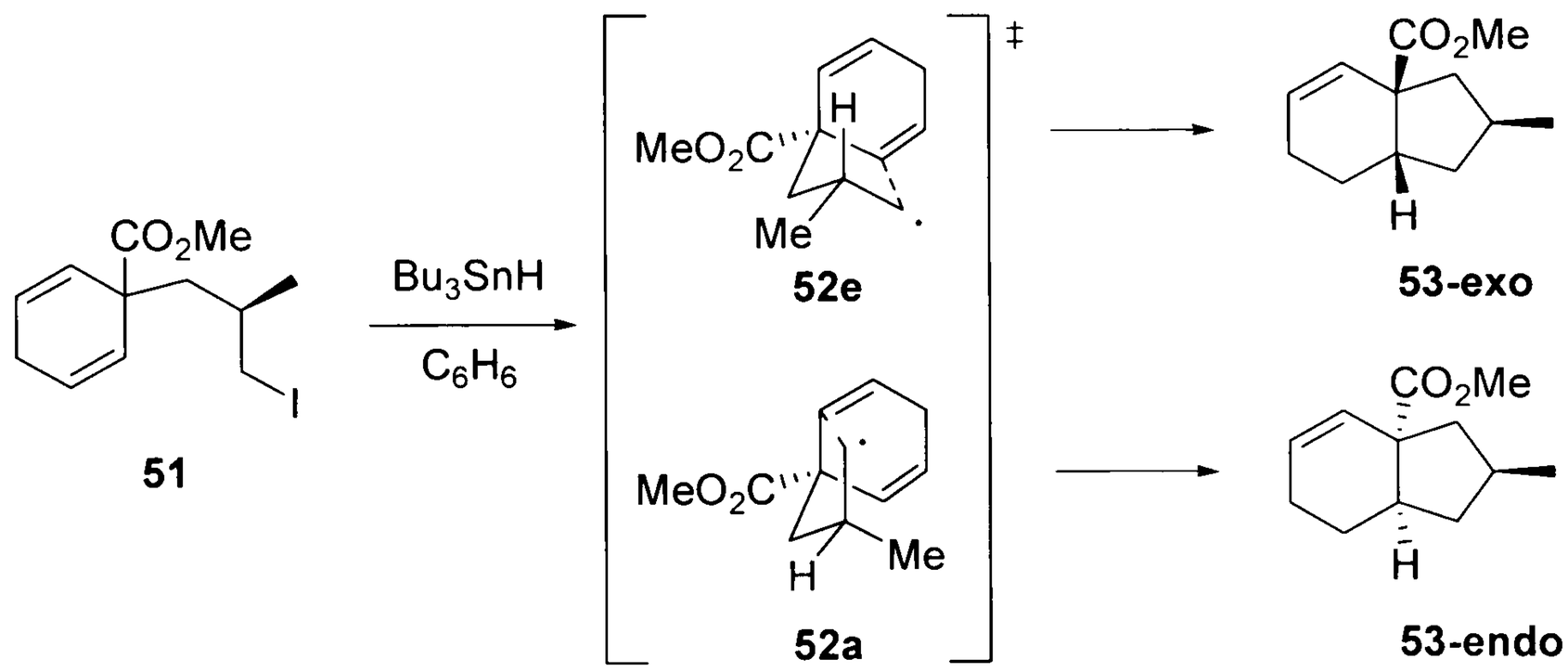
In the preferred transition state there is no clash between the pseudoequatorial R group and the axial isopropyl group on the silicon tether.

A wide array of desymmetrisation techniques have developed largely in response to problems associated with natural product synthesis. Wipf *et al* in 1992 reported the first example of a highly diastereotopic group selective intramolecular conjugate addition for the construction of hydroindolenone **50** (Scheme 15).[33]



Scheme 15

Curran and coworkers have surveyed diastereotopic group selective radical cyclisations, supporting computational predictions with experimental data.[22] A feature reaction is outlined in Scheme 16. Reductive cyclisation of **51** with tributyltin hydride provides **53-exo** and **53-endo** who selectivity is dependent upon the temperature of the reaction, from 30:1 (-78 °C) to 15:1 (80 °C).

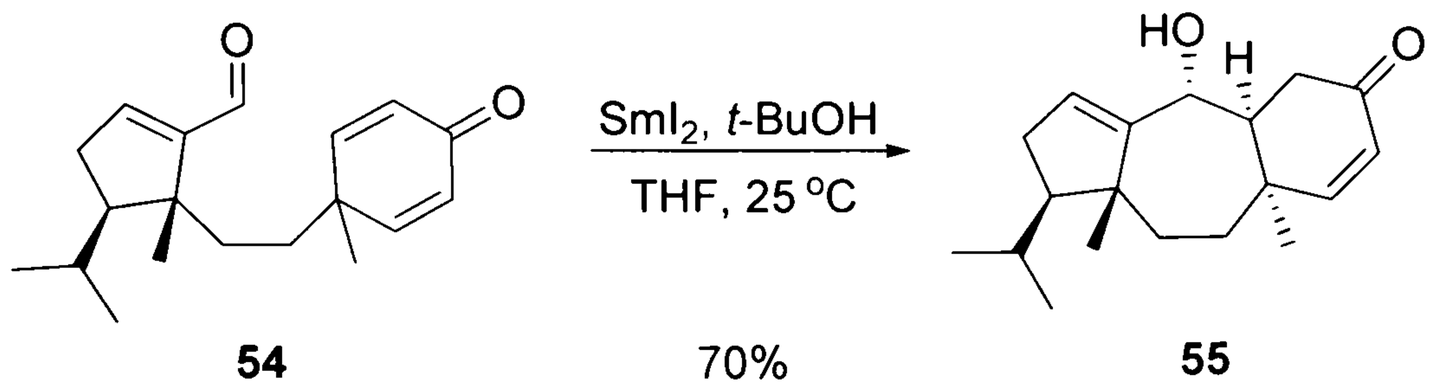


Scheme 16

The Beckwith-Houk model[34] was used to rationalise the selectivity for the 5-*exo*-cyclisation, where the radical **52** chooses between a chair-like transition state involving one olefin (**52e**) and an isomeric chair-like structure (**52a**) involving the other.

Lee and coworkers employ a group selective strategy to differentiate diastereotopic olefins to construct the 5-6-7 core of guanacastepenes (Scheme 17).[35] The diastereotopic double bonds are differentiated in the generation of the guanacastane tricycle **55** with the

desired *trans* stereochemical relationship between the methyl groups. This selectivity is proposed to be the consequence of a thermodynamically driven process.

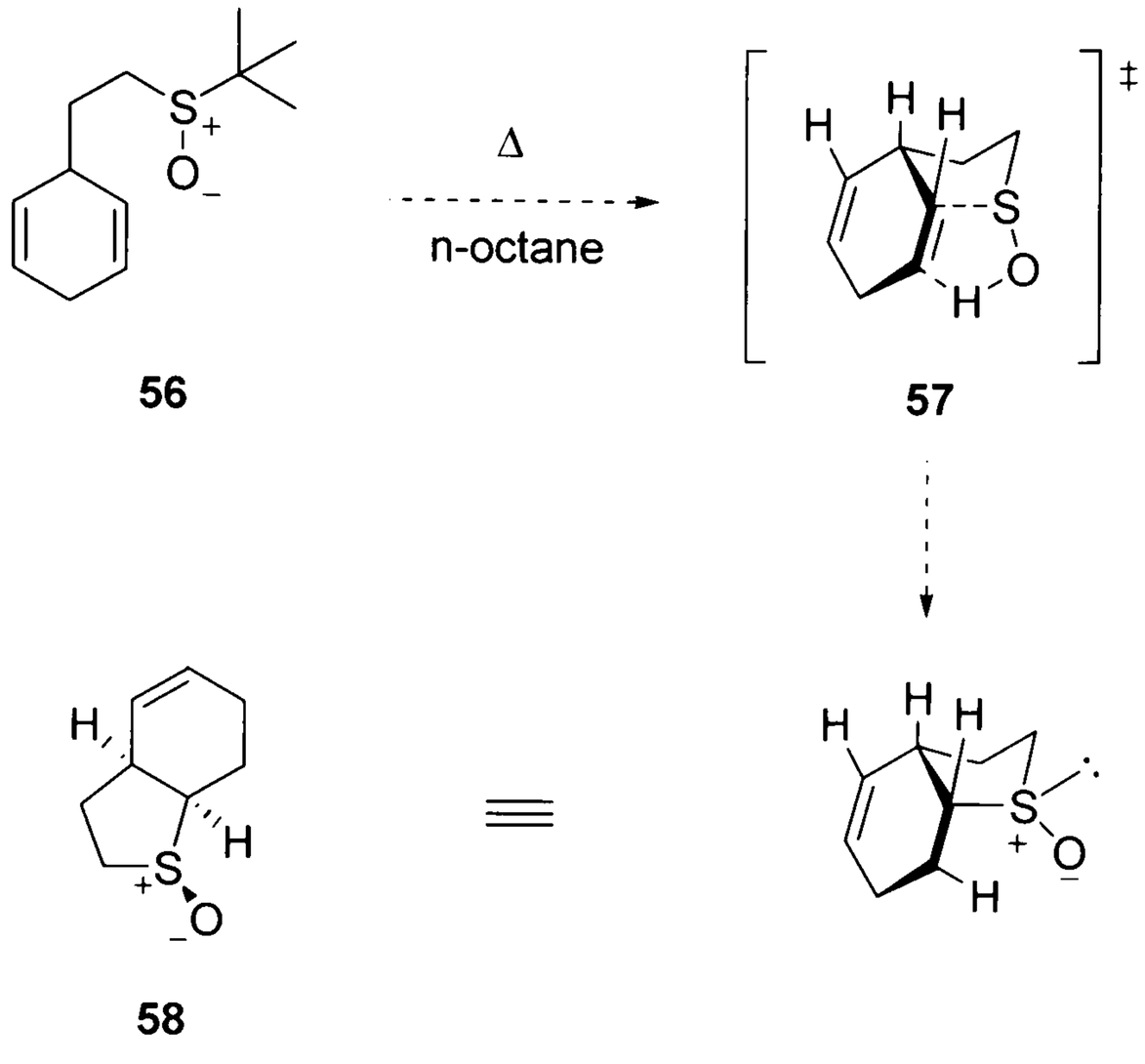


54 70% **55**

Scheme 17

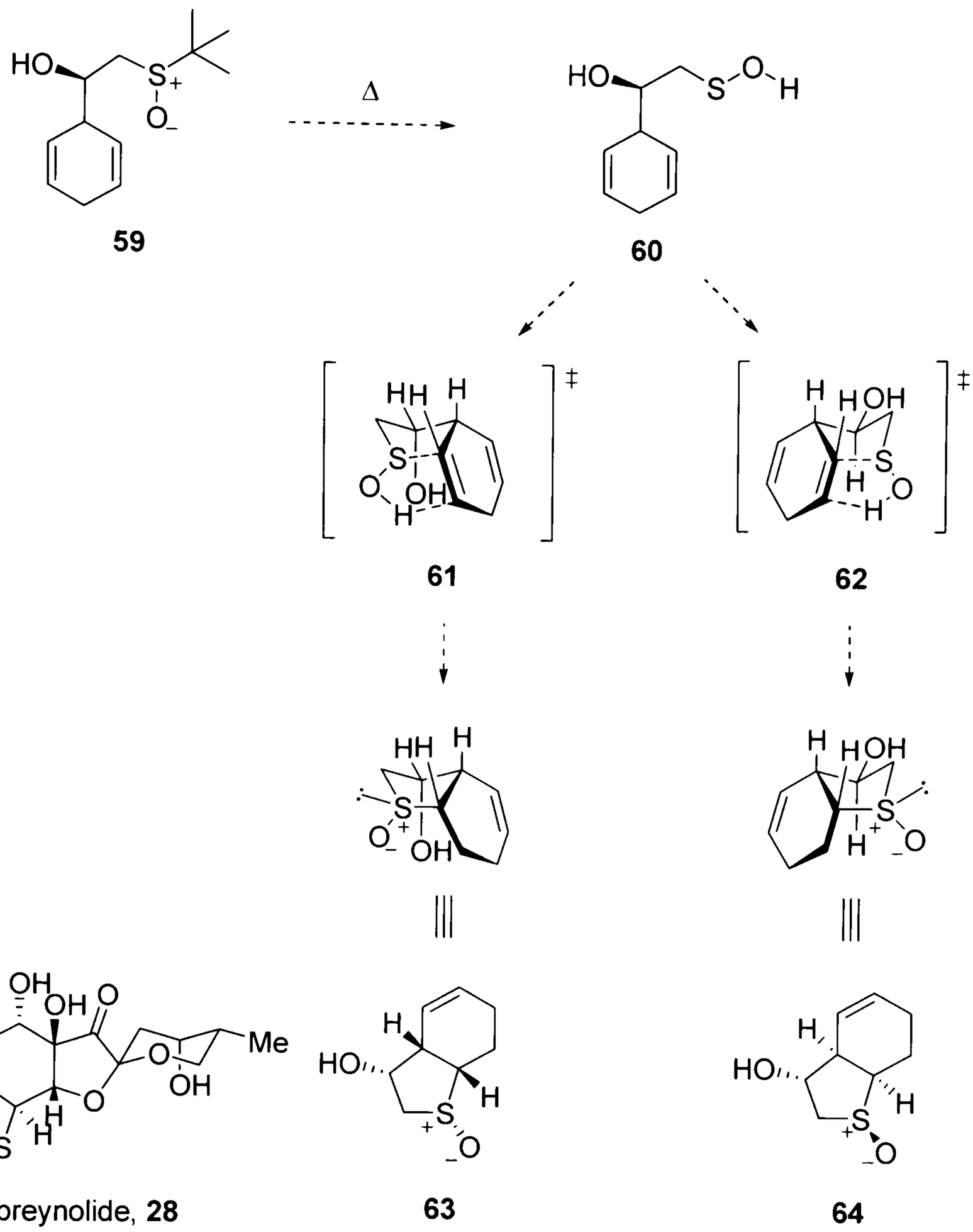
Section 1.5: Aims and objectives

Previous work within the Grainger group has involved attempts to extend the scope of the Jones sulfenic acid cyclisation to a stereocontrolled synthesis of perhydrobenzothiophene-S-oxide **58** (Scheme 18).[36]



Scheme 18

It was anticipated that thermolysis of *t*-butyl sulfoxide **56** should generate sulfenic acid **57** *in situ*, which in turn should cyclise onto one of the two double bonds to generate the cyclic sulfoxide **58**. This reaction should only furnish the *cis* ring junction due to the constraints of the 5-membered transition state leading to **58**, with a *trans* ring junction being geometrically impossible. Compound **58** represents a useful model system for the investigation of further synthetic transformations related to the synthesis of breynolide. It was intended to develop this methodology to study the effect of a suitably positioned chiral centre in the connecting side chain and in doing so to propose a new diastereotopic group selective cyclisation reaction (Scheme 19).



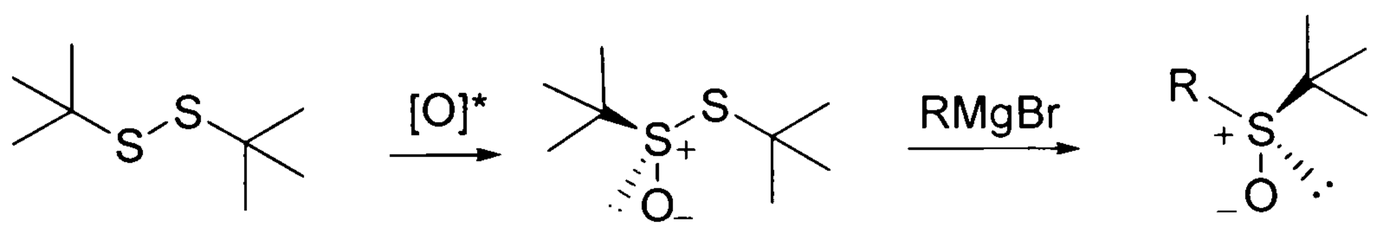
Scheme 19

Thermolysis of **59** should give rise to the formation of sulfenic acid **60**, which *via* intramolecular cyclisation onto one of the two prochiral double bonds should generate diastereoisomers **63** and/or **64**, through the diastereotopic transition states **61** and **62**.

The cyclic sulfoxides **63** and **64** differ only in the relative stereochemistry between the hydroxyl group and the three newly formed stereocentres. These three adjacent stereocentres in turn are set by the geometrical constraints of the transition state for sulfenic acid addition, by analogy with Jones system (Scheme 5), where a *trans* ring

junction is also sterically impossible. The intention therefore is for the hydroxyl group in the connecting chain to act as both stereochemical control element – controlling the relative amount of diastereoisomers **63** and **64** – and a source of the requisite oxygen functionality in breynolide **28**. Diastereoisomer **64** contains the same relative stereochemistry between the bridgehead hydrogens and hydroxyl functionality as found in breynolide **28**, although it was anticipated that either diastereoisomer should be equally useful if formed selectively due to the possibility of inverting the hydroxyl stereocentre in **63** via a Mitsunobu reaction.[37] Notably the transition state **62** leading to **64** places the hydroxyl substituent in a pseudo-equatorial position in the newly formed 5-membered ring, and hence is expected to be favoured over the alternative transition state **61** on steric grounds. Alternatively, transition state **61** may be favoured because intramolecular hydrogen bonding between the sulfenic acid and hydroxyl group may be possible.[38]

The methodology should allow for the preparation of all compounds enantiomerically pure, starting from non-racemic chiral sulfenic acid **60**. It was anticipated that this stereocentre, present in **59**, could be derived from enantiomerically pure *t*-butyl methyl sulfoxide. Methods exist for the preparation of enantiomerically pure *t*-butyl sulfoxides.[39] For example, Ellman has shown that asymmetrical oxidation of disulfide **65** with a chiral vanadium catalyst can provide sulfinate **66** in enantiomerically pure form.[40] Displacement with suitable Grignard reagents provides *t*-butyl sulfoxides **67** in enantiomerically pure form (Scheme 20).



65 **66** **67**

Scheme 20

The sulfoxide, enantiomerically pure, would first be used to set the alcohol stereochemistry in **59**, before being converted into a sulfenic acid in order to form the cyclic sulfoxide, in the process setting three new stereocentres. This overcomes one of the

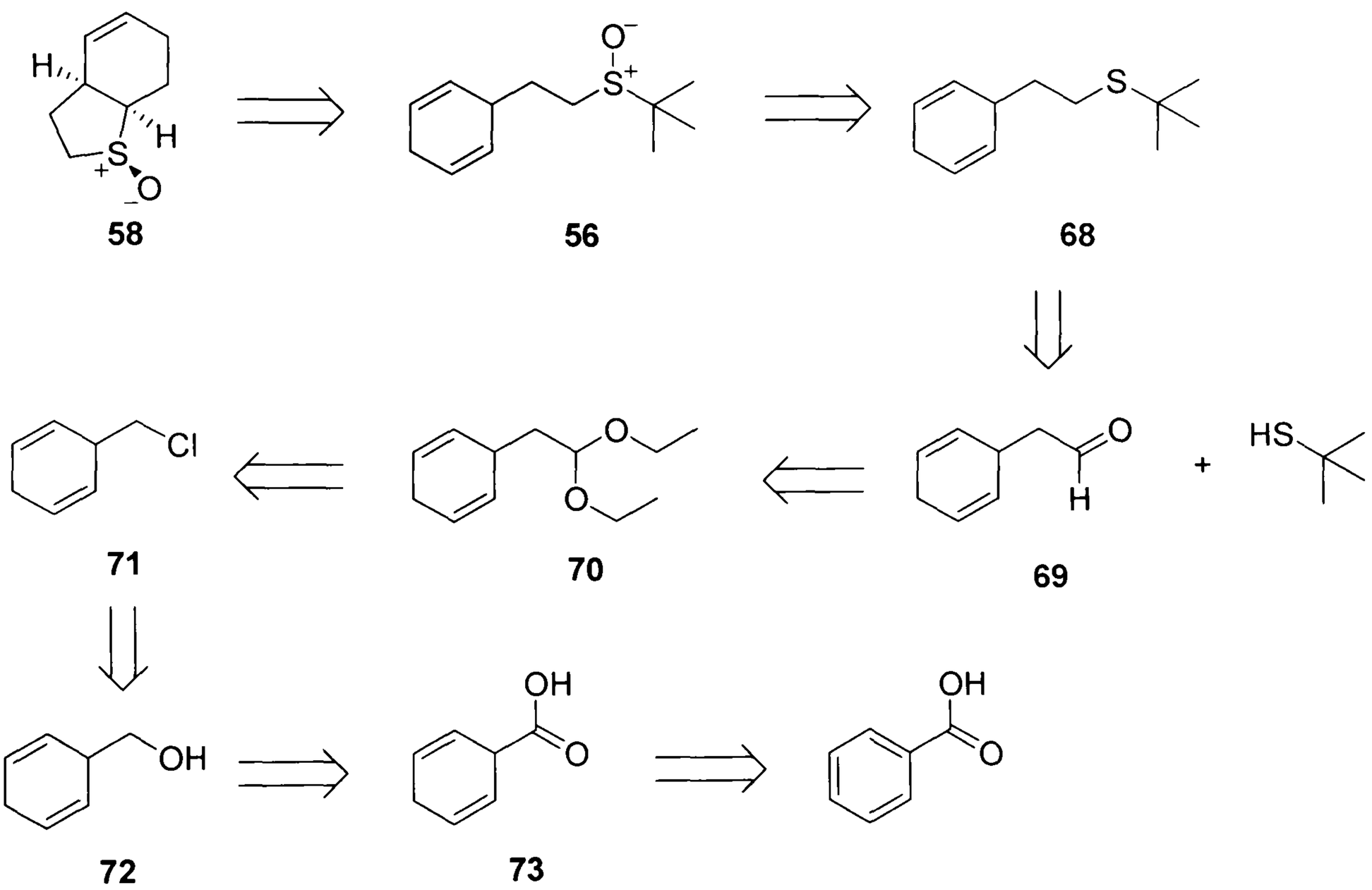
major drawbacks of the use of chiral sulfoxides in asymmetric synthesis, namely that chirality must be destroyed upon reductive removal or hydrolysis of sulfur.[41] In this case, four stereocentres would be derived from a single non-racemic chiral starting material. Finally, the sulfoxide oxygen acts as a protecting group for the readily oxidized sulfide, and as a potential stereodirecting group, in further synthetic transformations of **64** towards the synthesis of breynolide **28**.

Chapter 2

Section 2.1: Construction of the perhydrobenzothiophene system of breynolide

The addition of a sulfenic acid onto a diene ring to construct the perhydrobenzothiophene-S-oxide fragment of breynolide was first tested on a substrate bearing a sulfenic acid and a diene moiety tethered *via* an unsubstituted alkyl side chain.

The *t*-butyl sulfoxide **56** was chosen for initial investigation because it provided nine β-hydrogen atoms for the elimination, to optimise the formation of the intermediate sulfenic acid (Scheme 18). The synthesis of substrate **56** was based on earlier work conducted within the group for which a retrosynthetic outline is provided in Scheme 21.[36]



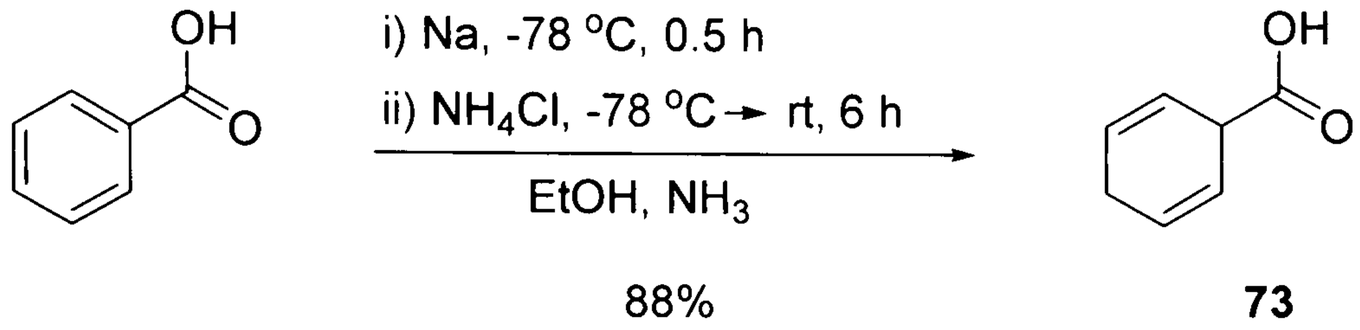
58 **56** **68** **71** **70** **69** **72** **73**

Scheme 21

The cyclisation precursor **56** could be made by oxidation of the sulfide **68**, which in turn can be derived from the known aldehyde **69** and *t*-butyl thiol, which is commercially available. The aldehyde **69** can be subsequently furnished *via* deprotection of the acetal **70**, which is readily synthesised from substrate **71**. The chloride **71** can be derived from alcohol **72**, which is the product of reduction of the carboxylic acid functionality of **73**.

The 1,3-diene **73** is in turn the Birch reduction product of commercially available benzoic acid.

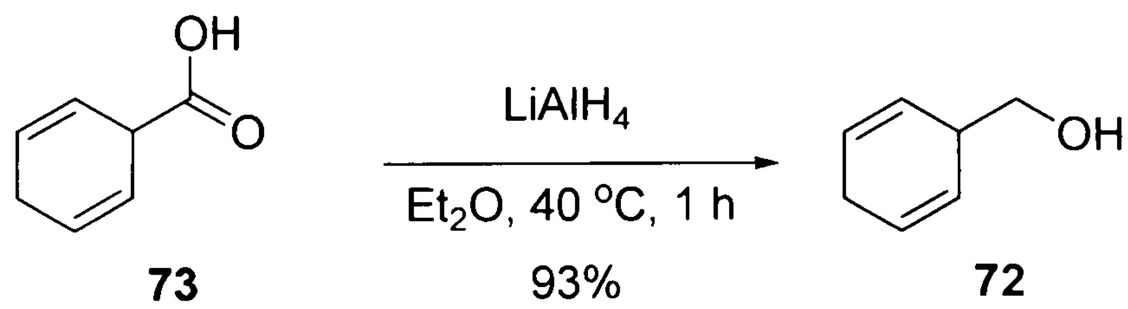
For the construction of **73** a Birch reduction[42] was performed on benzoic acid based on a sound literature precedent set by Kuehne and Lambert (Scheme 22).[43]



Scheme 22

The reduction of commercially available benzoic acid took place using sodium in liquid ammonia to afford 1,4-dihydrobenzoic acid **73** in good yield (lit.[43] 89-95%), which was deemed pure enough, as determined by ^{1}H NMR spectroscopy, to be used in the next step of the synthesis.

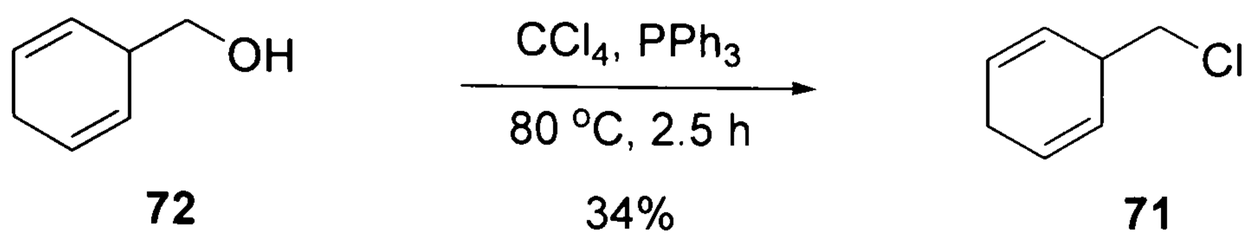
The carboxylic acid functionality of 1,4-dihydrobenzoic acid **73** was reduced with lithium aluminum hydride in anhydrous diethyl ether (Scheme 23).[44]



Scheme 23

The reaction was left to reflux for one hour to allow the starting material to be completely consumed as monitored by thin layer chromatography. The resulting alcohol **72** was isolated in excellent yield in comparison to that reported in the literature (lit.[44] 56%) and was again deemed pure enough to be carried through to the next step.

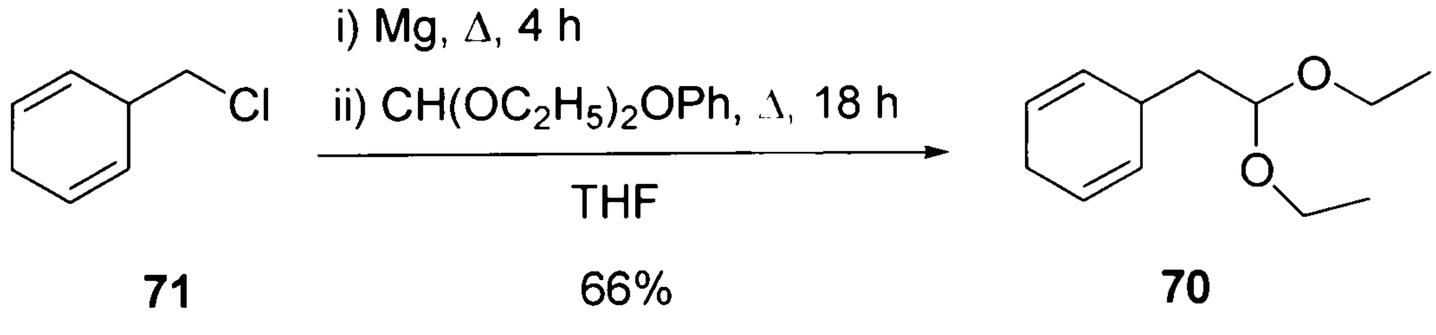
1,4-Dihydrobenzyl chloride **71** had previously been prepared in the literature from alcohol **72** using triphenylphosphine in carbon tetrachloride.[45] This procedure was therefore repeated for the synthesis of chloride **71** (Scheme 24).



Scheme 24

This step proved problematic due to difficulties in the removal of triphenylphosphine oxide by precipitation and filtration from the crude product **71** and as a result gave a low yield of the desired compound. An alternative procedure for the purification of **71** was found to be by short pad filtration with silica gel using 60-80 °C petroleum ether as eluent. The chloride was then further purified by Kugelrohr distillation (0.2 mm/Hg, 40-50 °C) to afford a colourless oil in 34% yield (lit.[45] 72%).

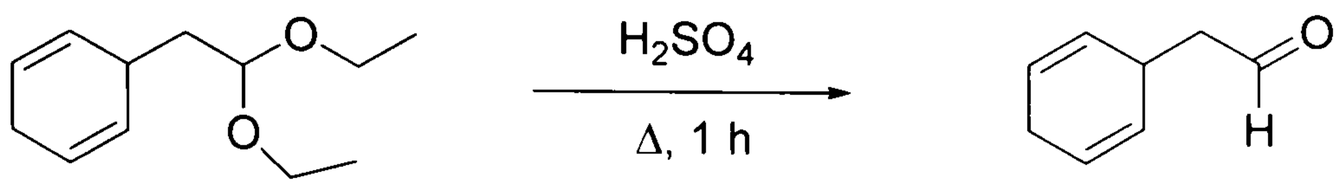
Reaction of 1,4-dihydrobenzyl chloride **71** with activated Mg in anhydrous tetrahydrofuran afforded the corresponding Grignard reagent (Scheme 25). This in turn was reacted with the electrophile diethyl phenyl orthoformate in refluxing tetrahydrofuran for 18 hours to give the corresponding acetal **70** in yields comparable to that reported in the literature (lit.[45] 68%).



Scheme 25

This material was deemed pure enough after work-up to be carried through to the next stage of the proposed synthesis.

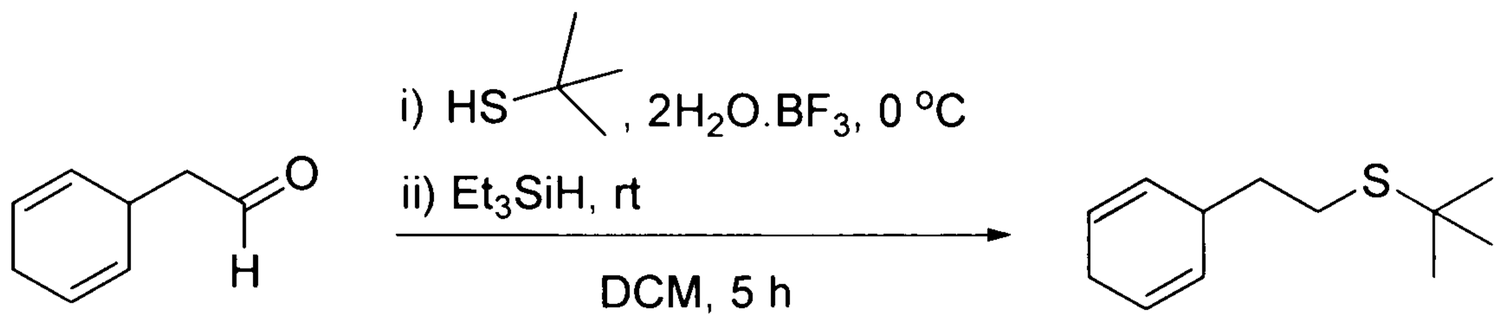
Acidic hydrolysis of the acetal **70** gave cyclohexa-2,5-dienyl-acetaldehyde **69** as a colourless oil in moderate yield (lit.[45] 71%), after purification by distillation (0.5mm/Hg. 120-140 °C), as depicted in Scheme 26.



70 49% **69**

Scheme 26

The direct reductive thiolation of the aldehyde **69** with *t*-butyl thiol catalysed by boron trifluoride dihydrate according to Olah's methodology[46] afforded the novel sulfide **68** as a colourless oil in almost quantitative yield (Scheme 27).

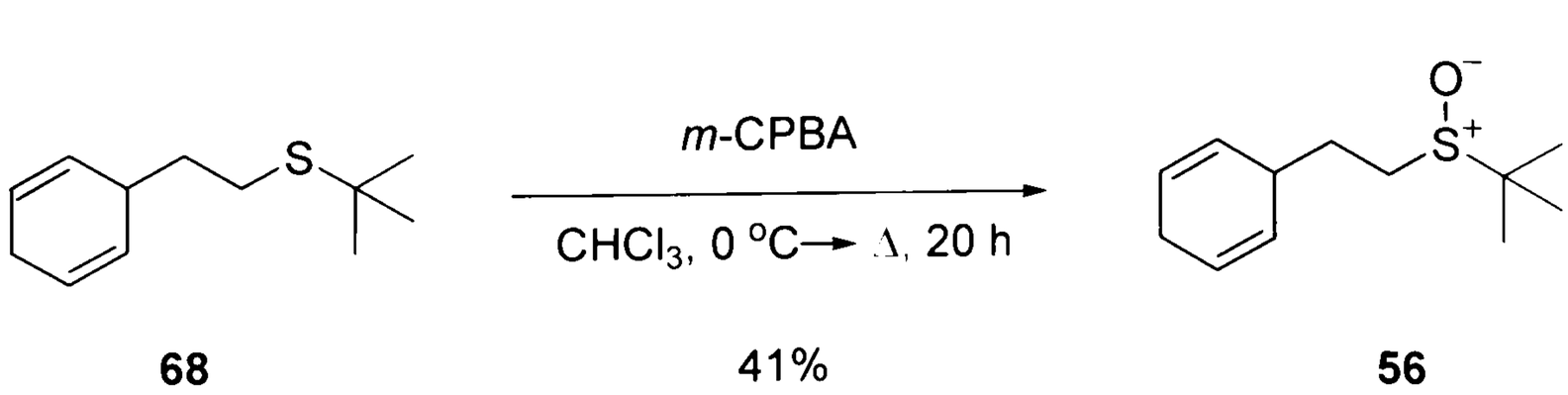


69 99% **68**

Scheme 27

The novel compound was characterised by ^{1}H and ^{13}C NMR, low and high resolution mass-spectrometry and IR spectroscopy.

The chemoselective oxidation of sulfide **68** was accomplished with *meta*-chloroperbenzoic acid as the oxidizing agent in chloroform (Scheme 28).

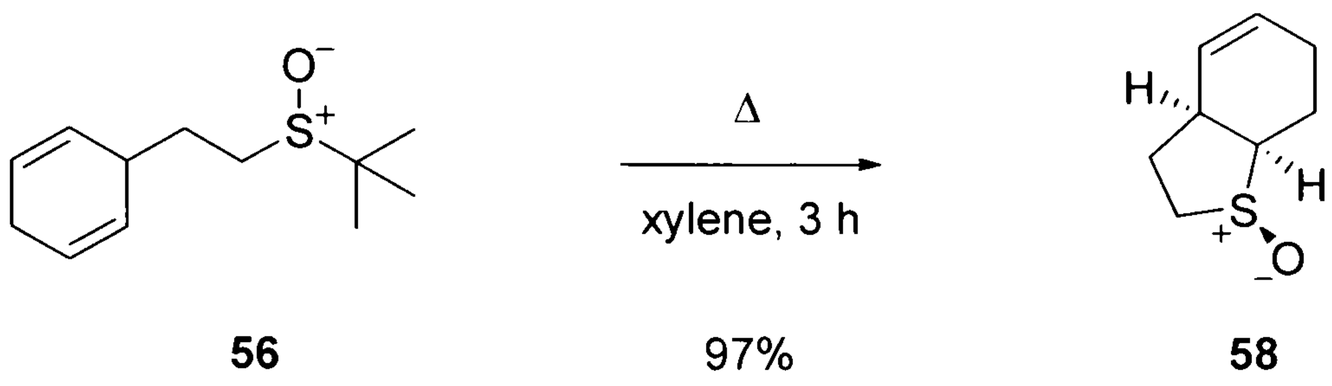


68 41% **56**

Scheme 28

The reaction afforded a crude oil which was then subjected to purification by column chromatography (2:8 diethyl ether/60-80 °C petroleum ether) to afford the sulfoxide **56** as a colourless oil in 41% yield, with 12% recovered starting material **68** and 7% of the undesired sulfone. The novel compound **56** was characterised by ^{1}H and ^{13}C NMR, low and high resolution mass-spectrometry and IR spectroscopy.

With the desired sulfoxide **56** in hand, the cyclisation precursor was submitted to Jones' thermolysis conditions, necessary to induce the elimination of sulfoxide (Scheme 29).



56 97% **58**

Scheme 29

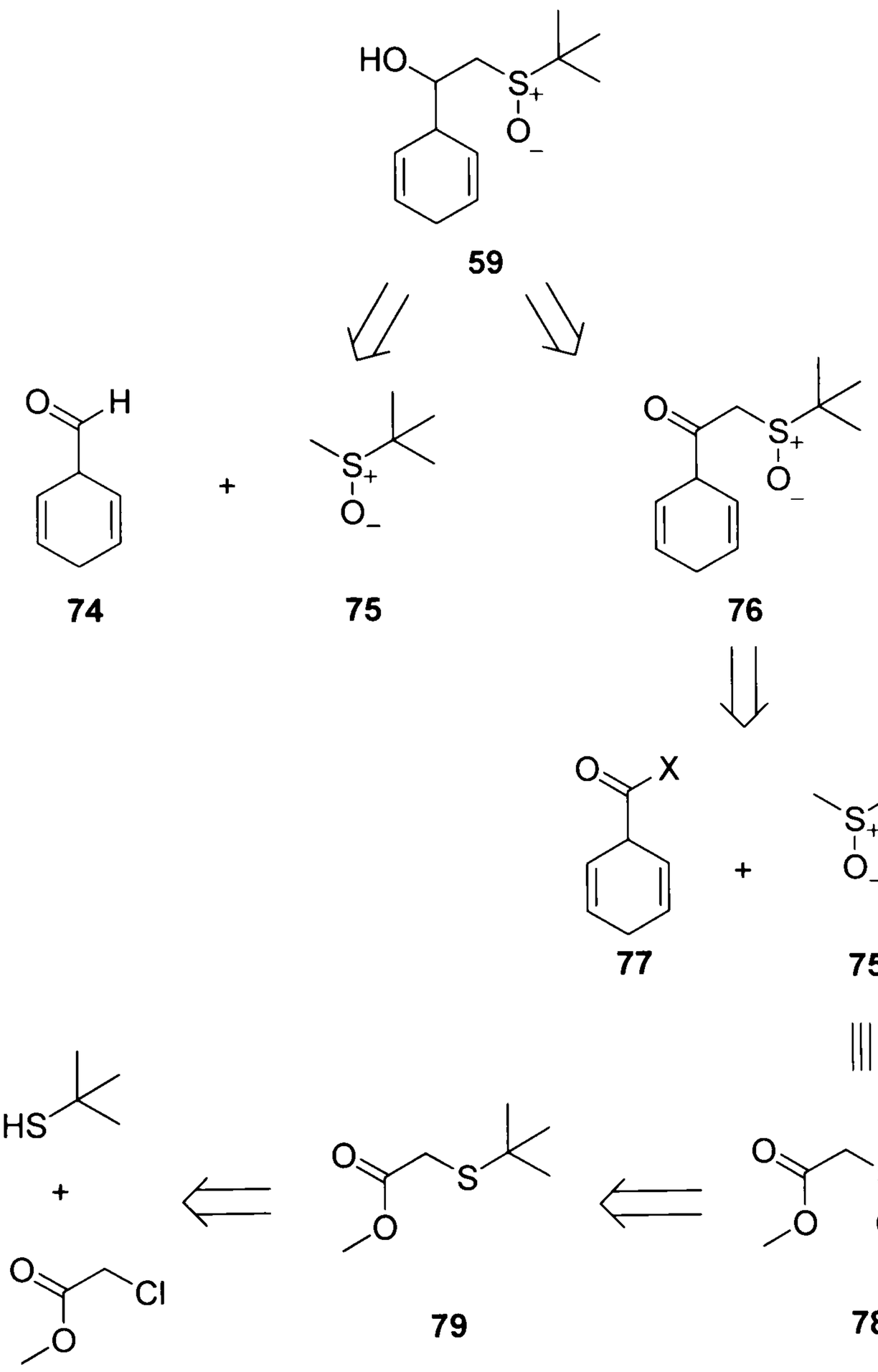
After 3 hours in refluxing xylene, the reaction mixture was subjected to column chromatography (1:9 methanol/diethyl ether) to remove xylene and to purify the resulting product. A single cycloadduct **58** was isolated as a colourless oil in essentially quantitative yield. The novel compound was characterised by ^{1}H and ^{13}C NMR, low and high resolution mass-spectrometry and IR spectroscopy. Detailed analysis of the NOESY spectrum of **58** confirmed the relative stereochemistry between the bridgehead hydrogens to be *cis* as expected. In fact, as depicted earlier in Scheme 18, the bridgehead hydrogens have to be *cis* to allow for the coplanarity of the 5 participating atoms in the proposed transition state **57**, as observed in the case of Jones system (Chapter 1, Section 1.2, Scheme 5).

Therefore, by the same argument, the sulfoxide stereochemistry was proposed to be as shown in **58**, opposite to the bridgehead hydrogens, although at this stage of the project this had yet to be unambiguosly determined.

As predicted, the tandem sulfoxide elimination – sulfenic acid addition of the substrate **56** generated only one cyclic diastereoisomer, characterised by three contiguous stereocentres, all of which are new and forced by the geometrical constraints of the transition state. The initial sulfoxide stereocentre is destroyed in the process of elimination to form the sulfenic acid intermediate and therefore can not be used to induce asymmetry in this specific system.

Section 2.2: Diastereoselective additions of sulfenic acids onto dienes

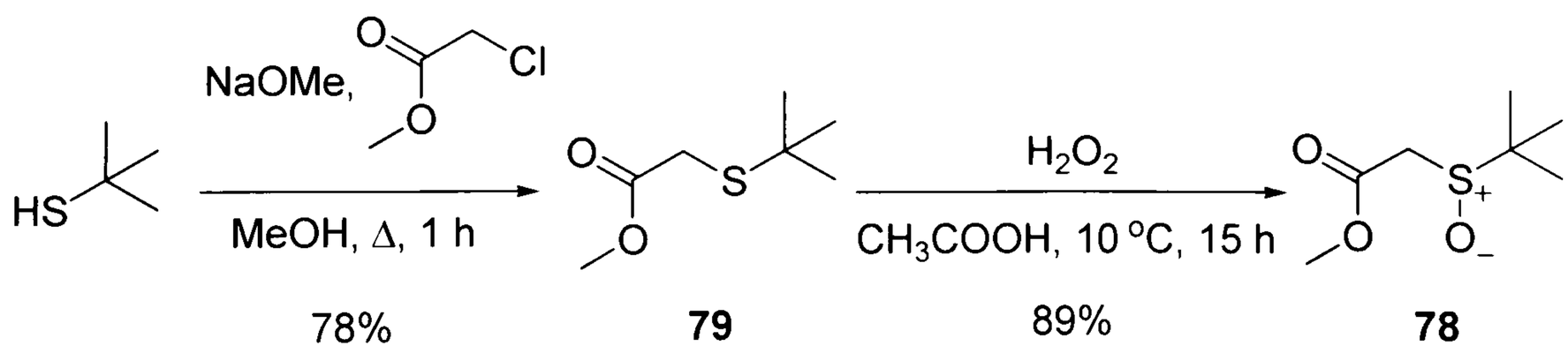
Having proved the success of the tandem sulfoxide elimination – sulfenic acid addition protocol for a stereocontrolled synthesis of perhydrobenzothiophene-S-oxide **58**, it was of interest to render the methodology diastereoselective by incorporation of a suitably positioned substituent on the connecting chain, specifically with a view to manipulate the substrate towards the synthesis of breynolide. A retrosynthetic outline for the initial target compound **59** is shown in Scheme 30.



Scheme 30

The key alcohol **59** is most simply disconnected back to aldehyde **74** and the anion of *t*-butyl methyl sulfoxide **75**. Aldehyde **74** is not known in the literature, and although previous work within the group had given promising results in terms of its synthesis,[36] an alternative approach to **59** was envisioned through reduction of ketone **76**. This approach is attractive in that reduction of β-keto sulfoxides is well known and conditions exist to favour the formation of either diastereoisomer.[47] Retrosynthesis of **76** suggested displacement of a leaving group X from an acid derivative **77** with the anion of *t*-butyl methyl sulfoxide **75**. However, previous work in the Grainger group had shown the failure of the anion of *t*-butyl methyl sulfoxide to displace leaving groups from similar dihydroderivatives to **77**. The recovery of apparently unreacted sulfoxide from these reactions was ascribed to the sulfoxide anion acting as a base rather than a nucleophile. To avoid the risk of having the sulfoxide anion of **75** acting as a base rather than a nucleophile, **78** is proposed as a synthetic equivalent of **75**. The ester group should reduce the basicity of the anion and can be potentially removed after the key C-C bond formation since β-keto esters are known to undergo decarboxylation. Sulfoxide **78** could derive from sulfide **79**, which in turn can be synthesised following a literature procedure by condensation of commercially available reagents *t*-butyl thiol and methyl chloroacetate.

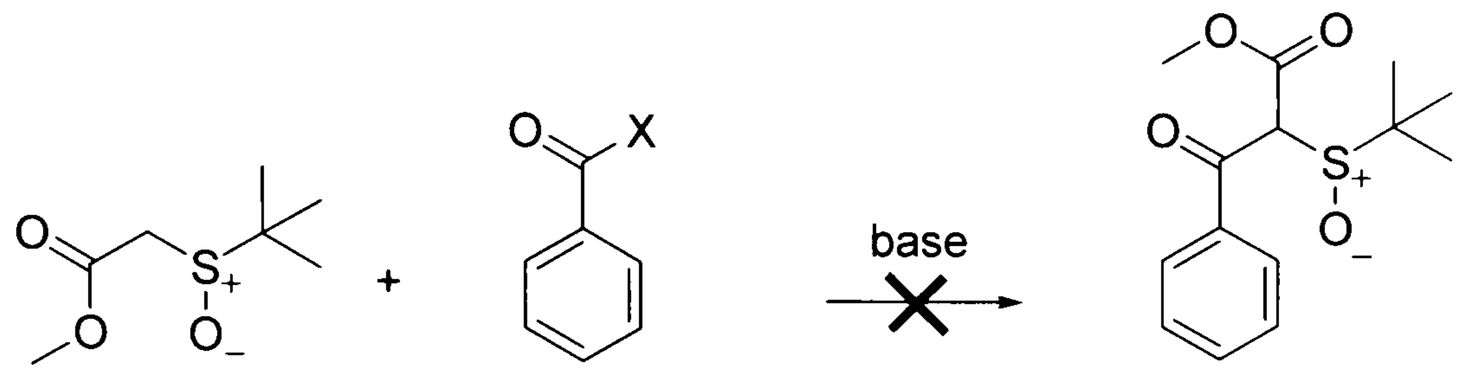
The synthesis of sulfoxide **78** was carried out following a literature procedure (Scheme 31).[48]



Scheme 31

Nucleophilic substitution of *t*-butyl thiol with methyl chloroacetate afforded methyl (2-methyl-2-propanethiol)-acetate **79** in good yield. Oxidation of sulfide **79** using hydrogen peroxide gave the desired sulfoxide **78** in 89% yield.[48]

The proposed condensation reaction between **78** and **77** was first tested on aromatic electrophiles **80** and **81** (Scheme 32).



78 X=Cl, **80** X=OEt, **81** **82**

Scheme 32

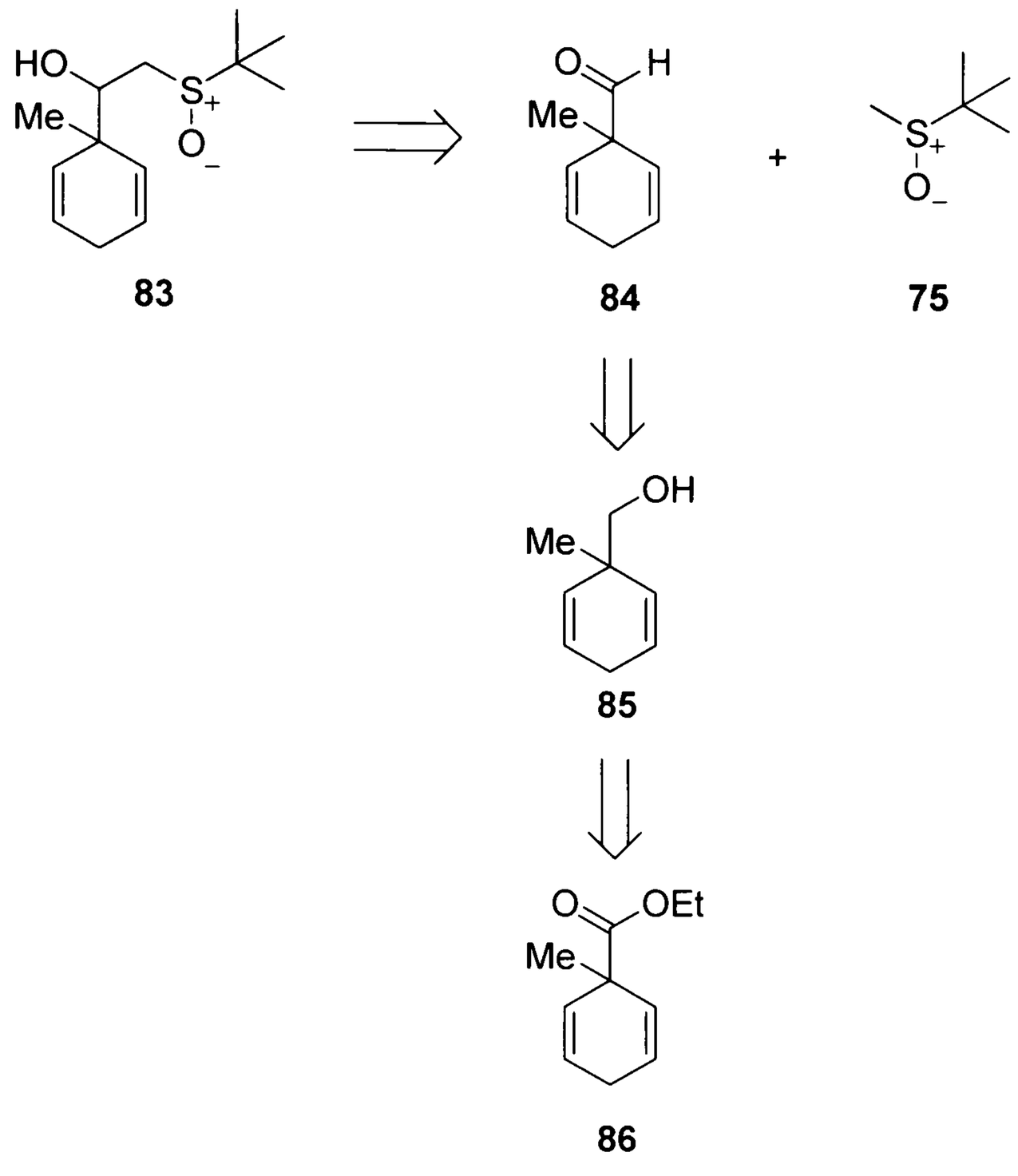
The results of the attempted reactions are summarised in Table 1.

Entry	**78**	electrophile	base	result
1	2 eq.	**80**, 1 eq.	NaH, 1 eq.	**78**
2	1 eq.	**80**, 1 eq.	LDA, 1.1 eq.	**78**
3	1 eq.	**81**, 2 eq.	EtMgBr, 1.3 eq.	**78**, **81**
4	1 eq.	**81**, 2 eq.	EtMgBr, 2.6 eq.	**78**, **81**
5	1 eq.	**81**, 1 eq.	NaOMe, 2.5 eq.	**78**, **81**
6	1 eq.	**81**, 2 eq.	*t*-BuMgBr, 2.6 eq.	**78**, **81**
7	2 eq.	**81**, 1 eq.	NaH, 1 eq.	/
8	1 eq.	**81**, 1 eq.	LDA, 2 eq.	**78**
9	2 eq.	**81**, 1 eq.	LDA, 2 eq.	/

Table 1

Different bases and conditions were tried to generate the anion of **78**.[49] In general the reactions gave recovery of starting material only (Table 1, entries 1-6 and entry 8).

Having failed in the attempt to synthesise compound **82**, an alternative target compound was proposed to test the group selective cyclisation reaction (Scheme 33).



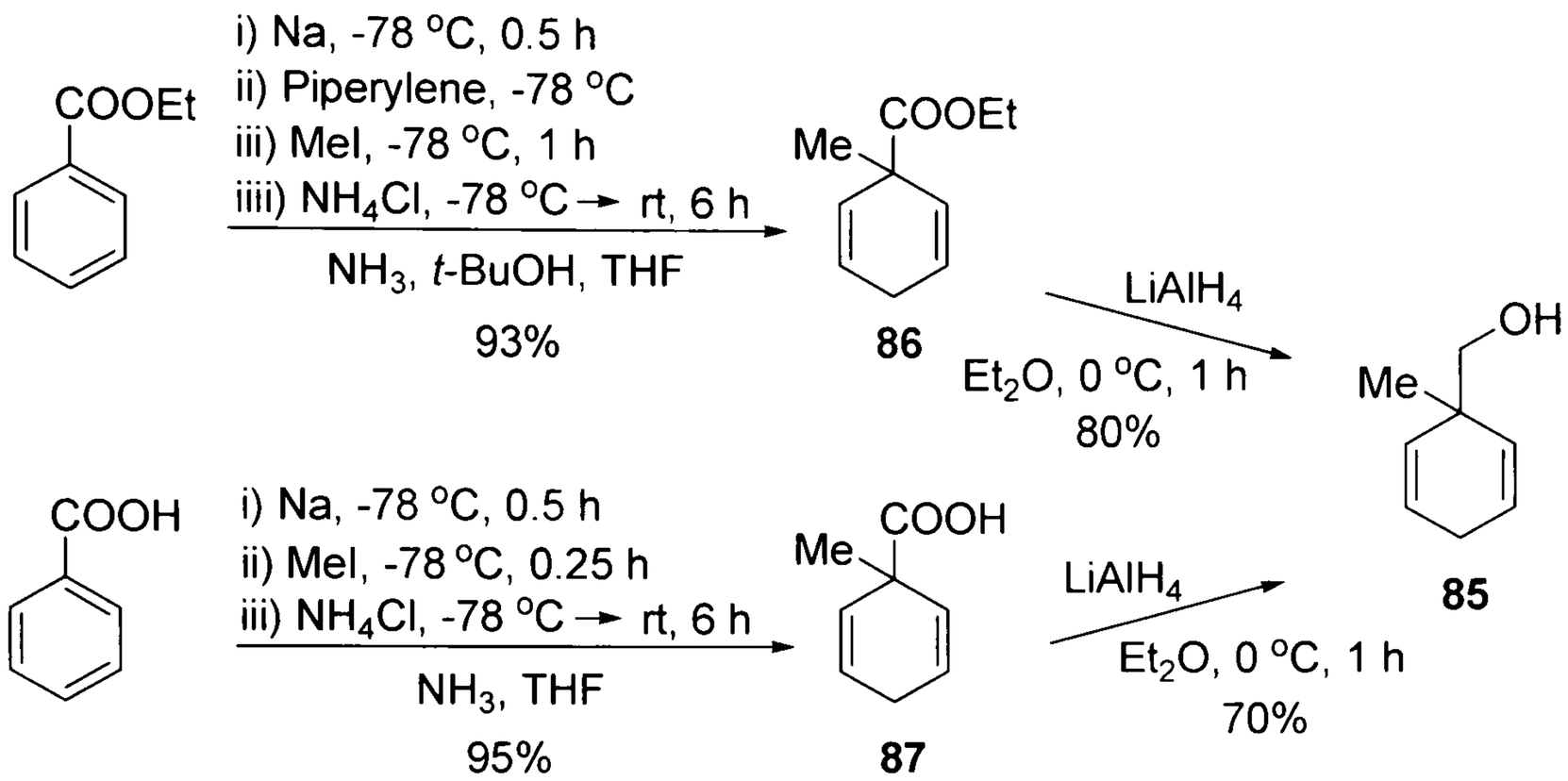
Scheme 33

Alcohol **83** has an additional methyl group compared to the model substrate **59** presented earlier. Although the methyl group at the *ipso* position is not required for the synthesis of breynolide, it should greatly aid the synthesis of the cyclisation precursor **83**, in that it prevents deprotonation at this highly acidic site and subsequent re-aromatisation of the dehydrobenzene ring. Furthermore, the presence of the methyl group does not interfere with the proposed investigation as to whether having a stereocentre in the connecting chain can control the addition of a sulfenic acid onto one of the (still) prochiral double bonds. However, this may obviously have an effect on the selectivity, and indeed this will be demonstrated.

Disconnection of the ß-hydroxy sulfoxide **83** furnished aldehyde **84** and sulfoxide **75** (*vide supra*). The preparation of this aldehyde should be possible from oxidation of the corresponding alcohol **85**, which in turn could be prepared from the carboxylic acid ester

86. The ester **86** could be synthesised from commercially available ethyl benzoate by Birch reduction and *in situ* trapping of the resulting anion with methyl iodide.

Two approaches to the synthesis of alcohol **85** have been developed and are outlined in Scheme 34.



Scheme 34

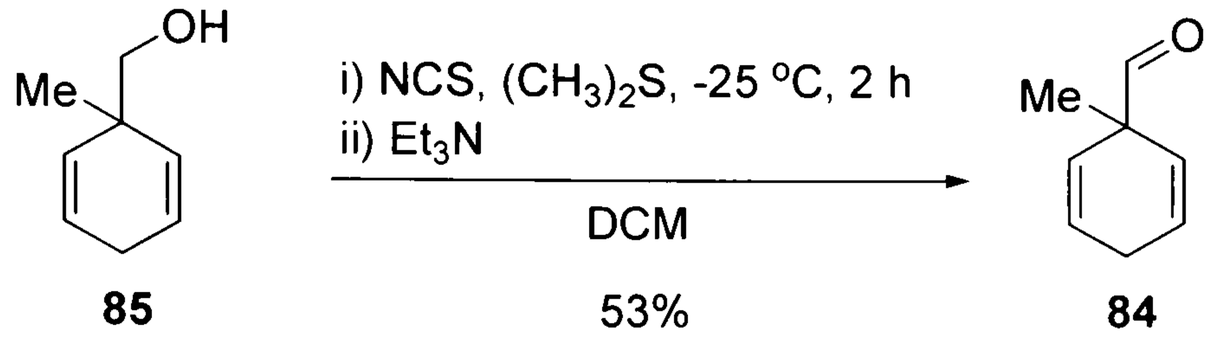
Birch reduction of ethyl benzoate followed by a quench of the resulting anion with the electrophile methyl iodide provided the novel ester **86** in 93% yield.[50] Diene **86** was characterised by ^{1}H and ^{13}C NMR and IR spectroscopy, although mass-spectrometry did not identify the compound.

The reduction of the ester functionality was accomplished using lithium aluminum hydride and the reaction afforded the desired alcohol **85** in good yield.[50] Alcohol **85** was also prepared *via* reduction of the corresponding acid **87** with lithium aluminum hydride.[51]

The carboxylic acid **87** was derived from Birch reduction of the commercially available benzoic acid and a resultant quench of the anion with methyl iodide.[51] Despite the slightly higher yield for the latter reduction, a cleaner product was obtained from the reduction of

ester **86** after a standard work-up and hence the former reaction was the method of choice for the synthesis of alcohol **85**.

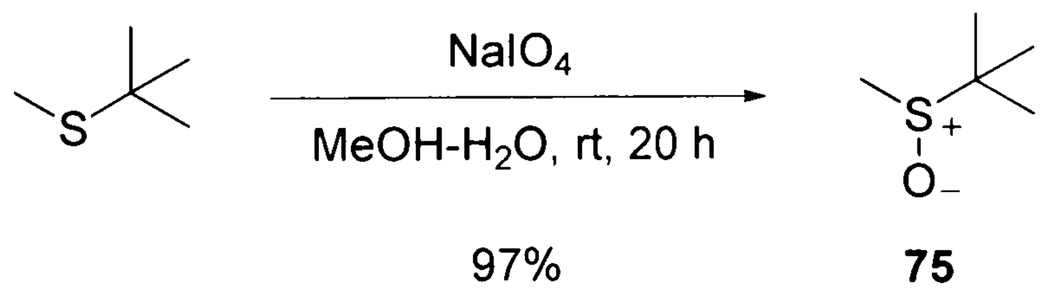
The alcohol **85** was then carried through to the next step, the synthesis of aldehyde **84** (Scheme 35).



Scheme 35

Following the Corey-Kim modification of the Swern protocol,[51] the alcohol **85** was oxidised to the corresponding aldehyde **84**. The crude aldehyde was subjected to purification by distillation (0.4 mmHg, 20-40 °C) to afford compound **84** as a colourless oil.

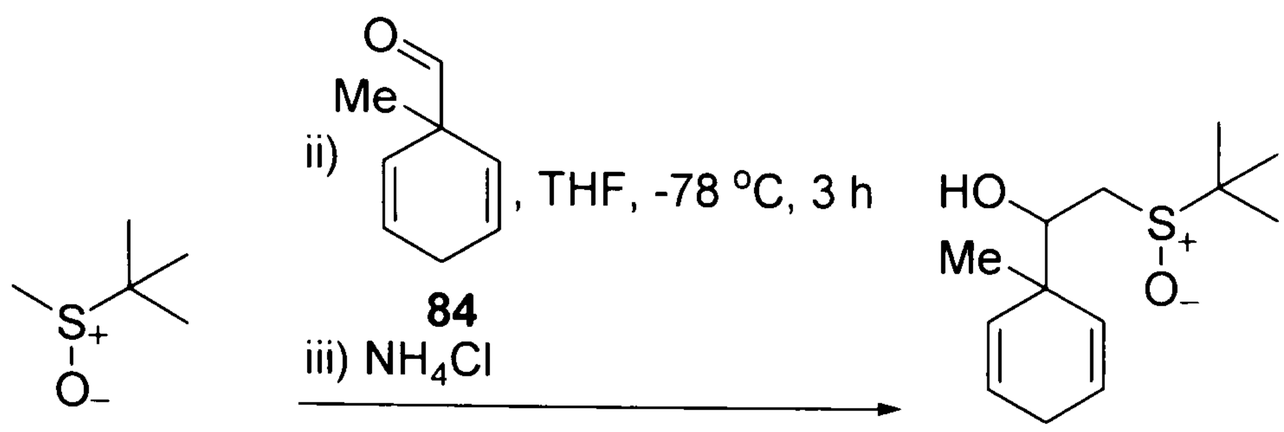
The desired partner for the convergent synthesis of sulfoxide **83**, *t*-butyl methyl sulfoxide **75**, was synthesised from commercially available *t*-butyl methyl sulfide as depicted in Scheme 36. [52]



Scheme 36

Oxidation of the sulfide with sodium periodate gave the desired sulfoxide in excellent yield and without the need for further purification.

Condensation of the anion of *t*-butyl methyl sulfoxide **75** with aldehyde **84** afforded the desired alcohol **83**, as shown in Scheme 37.

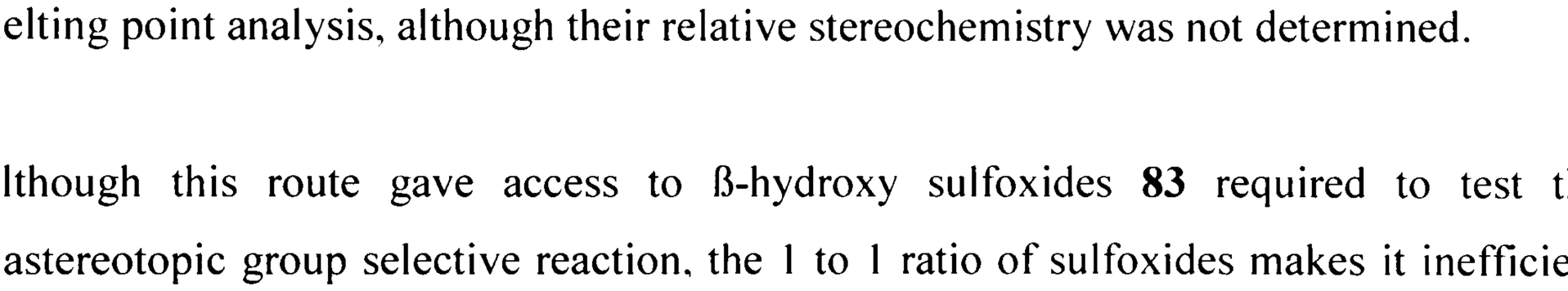


75 62% (dr 1:1) **83**

Scheme 37

The sulfoxide **75** was allowed to react with lithium diisopropylamide at -78 °C to form the stabilised anion before the addition of aldehyde **84** to the reaction flask. The reaction resulted in a mixture of diastereomeric alcohols **83**, which were separable by column chromatography (diethyl ether, **83a**, $R_f = 0.4$ and **83b**, $R_f = 0.1$). The products are present in a ratio of 1 to 1, typical selectivity observed for the addition of sulfoxide anions to aldehydes.[41] The solid diastereoisomers, **83a** and **83b**, were fully characterised *via* ^1H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry, IR spectroscopy and melting point analysis, although their relative stereochemistry was not determined.

Although this route gave access to ß-hydroxy sulfoxides **83** required to test the diastereotopic group selective reaction, the 1 to 1 ratio of sulfoxides makes it inefficient for accessing enantiomerically pure compounds *via* a chiral relay from enantiomerically pure *t*-butyl methyl sulfoxide. In order to overcome this problem, an alternative strategy would be to react **86** with **75** and then stereoselectively reduce the ketone functionality of **88**. The idea is outlined in Scheme 38.

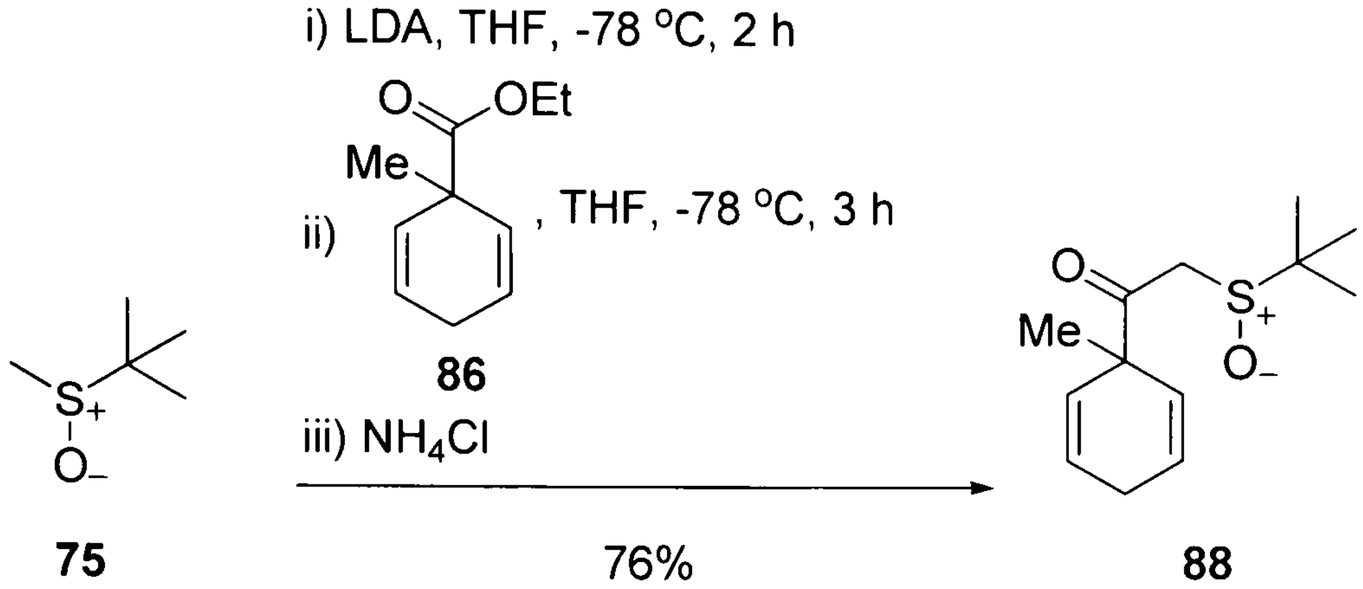


83 **88** **86** **75**

Scheme 38

The two partners of the coupling **86** and **75** have already been synthesised for use in the previous approach as outlined in Scheme 33.

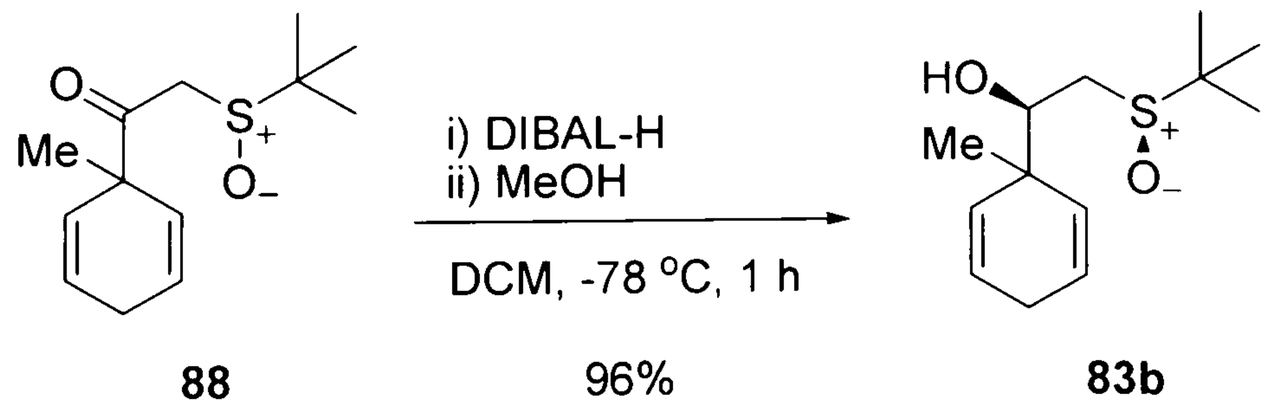
The condensation of **75** with **86** gave the desired product **88** in good yield (Scheme 39).[49]



Scheme 39

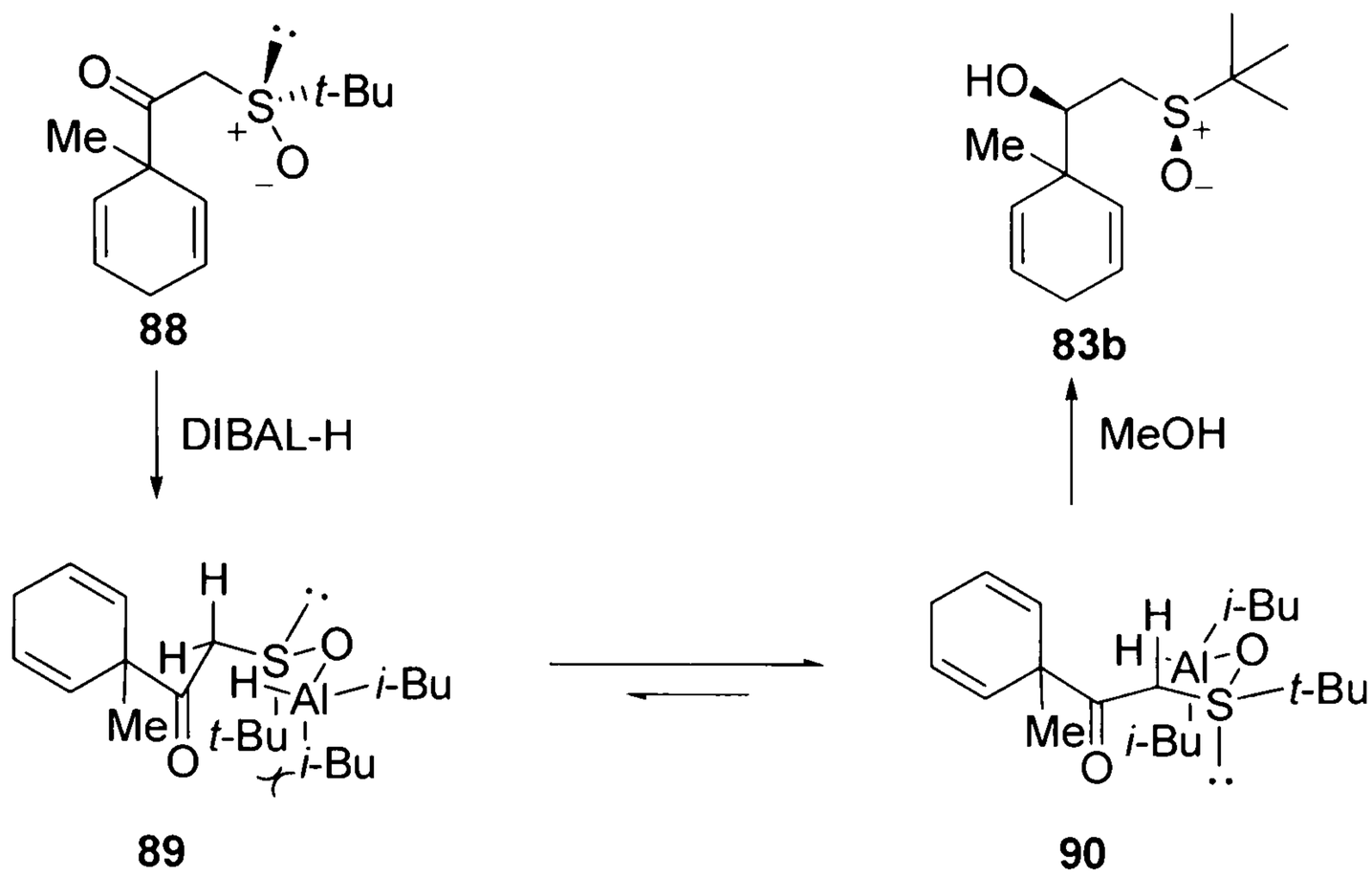
The ester **86** was coupled with 2 equivalents of the anion of *t*-butyl methyl sulfoxide **75** to provide ß-keto sulfoxide **88**. Two equivalents of the nucleophile **75** are necessary to allow 1 equivalent of the electrophile **86** to be fully consumed, since the product **88** is itself susceptible to deprotonation by the anion of **75**. The crude product was purified by column chromatography (diethyl ether) to afford the novel compound as a colourless oil. The ß-keto sulfoxide **88** was characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry and IR spectroscopy.

The sulfoxide **88** was then subjected to chemo- and stereoselective reduction (Scheme 40).



Scheme 40

The diastereoselective reduction of sulfoxide **88** was accomplished using the bulky electrophilic reducing agent diisobutylaluminum hydride; that selectively drove the reaction towards the *trans* ß-hydroxy sulfoxide **83b** in almost quantitative yield.



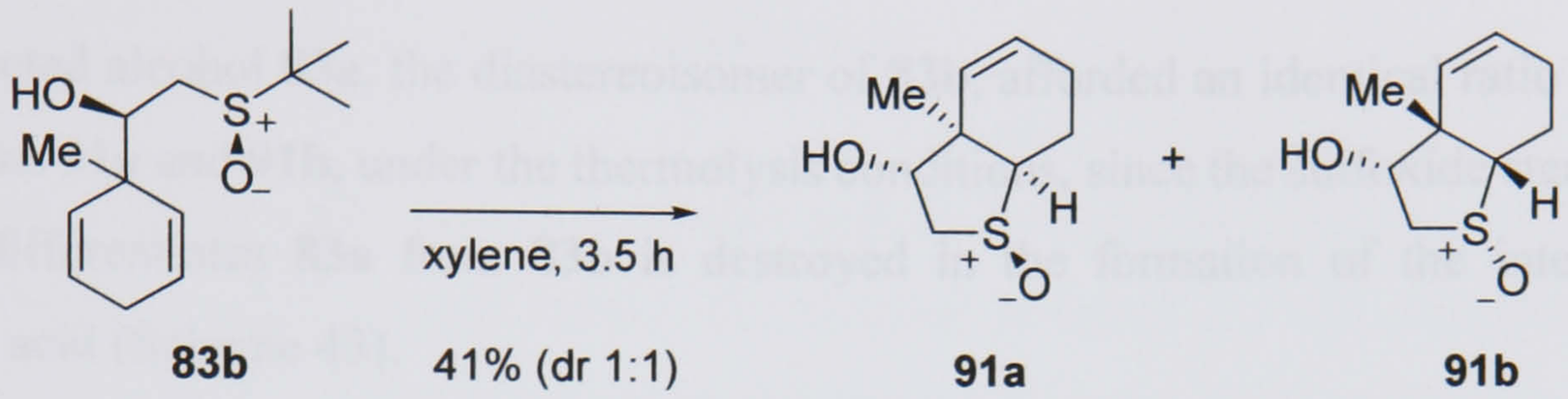
Scheme 41

The resulting relative stereochemistry is explained by Solladié *et al*, who suggested that the conformation **90**, where diisobutylaluminum hydride attacks the less hindered face of ketone **89**, is the more energetically favoured one (Scheme 41).[47] The opposite sense of selectivity would be observed if zinc chloride, acting as a Lewis acidic chelating agent between the keto and sulfoxide functionalities, would have been added to the reaction.

The relative stereochemistry of **83b** was then determined as *trans* by correlation to the resulting product of the reduction of **88** and comparison of the respective ^{1}H NMR spectra. Although the relative stereochemistry between the alcohol and the sulfoxide is not important in the racemic series since the sulfoxide stereocentre is destroyed in the process of elimination to the sulfenic acid intermediate, it is important for accessing enantiomerically pure material, as this reaction sets the stereochemistry of the hydroxy centre, the only stereocentre present in the intermediate of the cyclisation reaction.

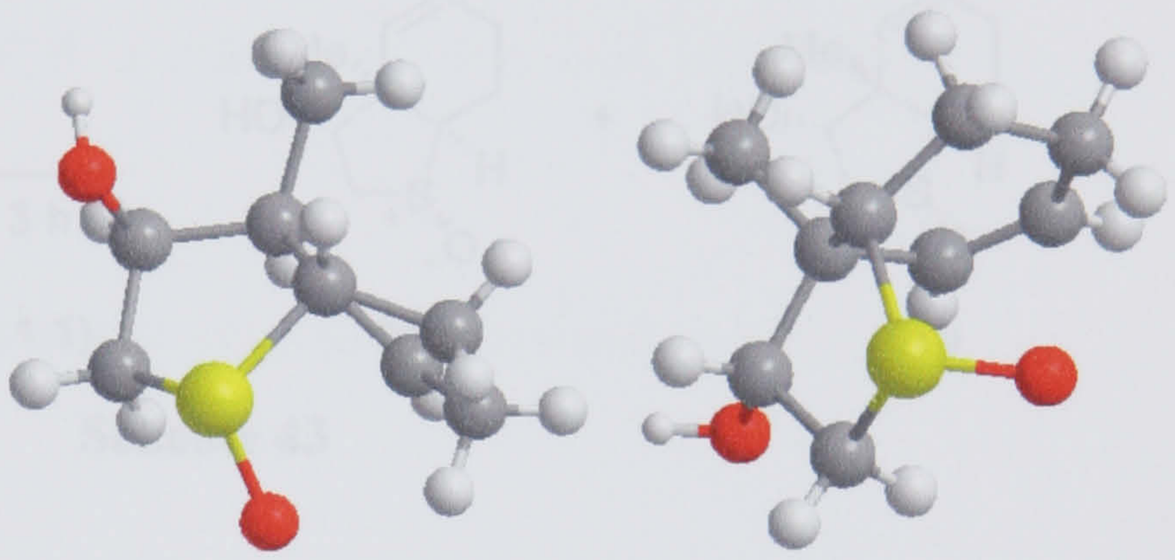
Section 2.3: Diastereotopic group selective intramolecular cycloadditions of sulfenic acids to 1,4-dienes

The alcohol **83b** was subjected to the standard thermolysis conditions shown in Scheme 42.



83b 41% (dr 1:1) **91a** **91b**

Scheme 42



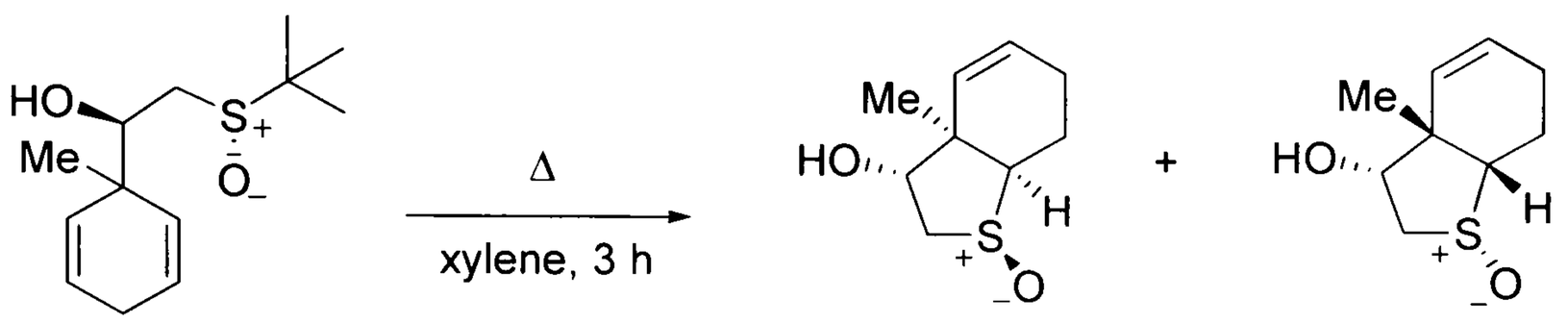
91a **91b**

Figure 6

Refluxing ß-hydroxy sulfoxide **83b** in xylene for 3.5 hours afforded a mixture of just two cyclic sulfoxides **91a** and **91b**, but in a ratio of 1:1. Purification by column chromatography (4:96 methanol/diethyl ether) allowed for the separation of the two diastereoisomers and isolation of 14% of recovered starting material. Leaving the reaction for a longer period of time, in an attempt to consume the starting material **83b**, resulted in the thermal decomposition of products **91a** and **91b**. The novel compounds were fully characterised by ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry, IR spectroscopy and melting point analyses. The structures of the two perhydrobenzothiophene-S-oxides were also unambiguously determined by X-ray crystallography (Figure 6 and Appendices 6.1 and 6.2), since extensive analysis of NOESY spectra failed to determine the relative stereochemistry between the alcohol and

the remaining three stereocentres in each case. Both **91a** and **91b** crystallise in a conformation in which the sulfoxide oxygen and bridgehead methyl groups occupy pseudo-equatorial positions on the thiolane ring, with the alcohol pseudo-axial in **91a** and pseudo-equatorial in **91b**.

As expected alcohol **83a**, the diastereoisomer of **83b**, afforded an identical ratio of cyclic sulfoxides **91a** and **91b**, under the thermolysis conditions, since the sulfoxide stereocentre which differentiates **83a** from **83b** is destroyed in the formation of the intermediate sulfenic acid (Scheme 43).

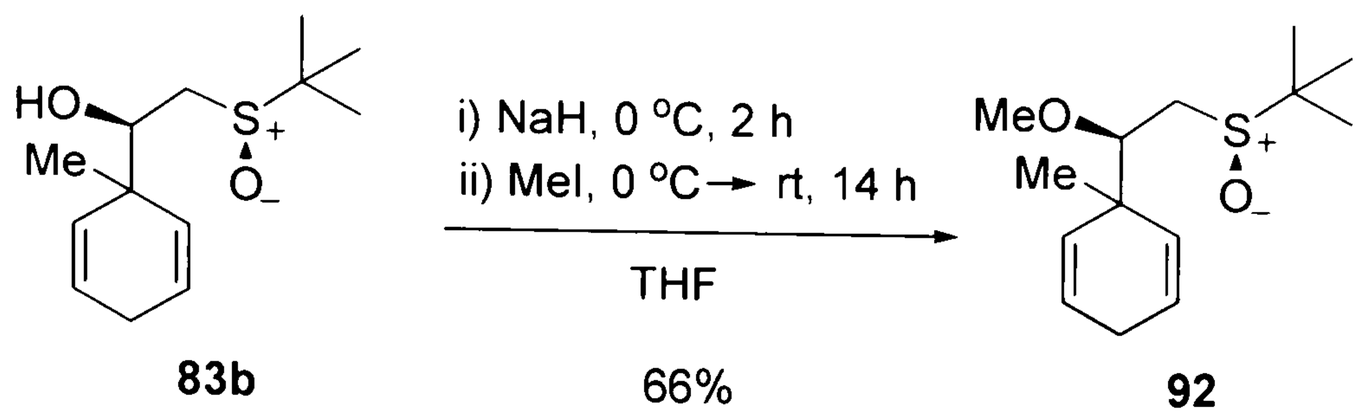


83a 57% (dr 1:1) **91a** **91b**

Scheme 43

Although it has been proven that the free hydroxyl group in substrate **83b** can be tolerated in the cyclisation, the stereocentre has no control over the selectivity of the process. However, it was thought that the ratio of diastereoisomers might be influenced by the nature of the substituent on oxygen. To this end, alcohol **83b** was protected with a variety of groups of various steric and electronic character under the conditions outlined in Schemes 44 to 49.

The free hydroxyl group was alkylated as its corresponding methyl ether as shown in Scheme 44.

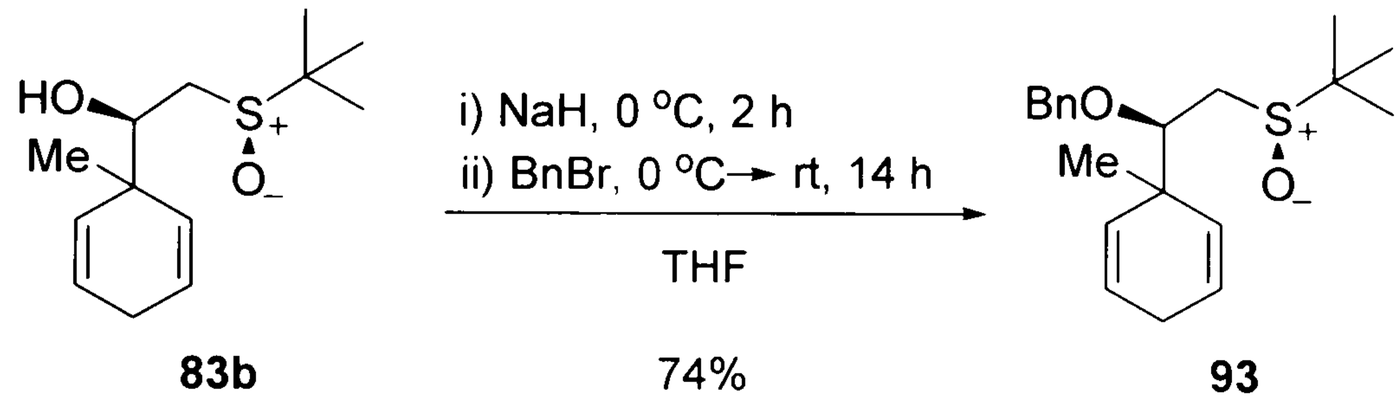


83b **92**

Scheme 44

ß-Hydroxy sulfoxide **83b** was reacted with sodium hydride for 2 hours at 0 °C before adding the electrophile methyl iodide. The reaction afforded a crude compound which was purified by column chromatography (7:3 diethyl ether/60-80 °C petroleum ether) to afford the desired substrate **92** as a colourless oil. The novel compound **92** was fully characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry and IR spectroscopy.

The alcohol **83b** was alkylated as its benzyl ether as depicted in Scheme 45.

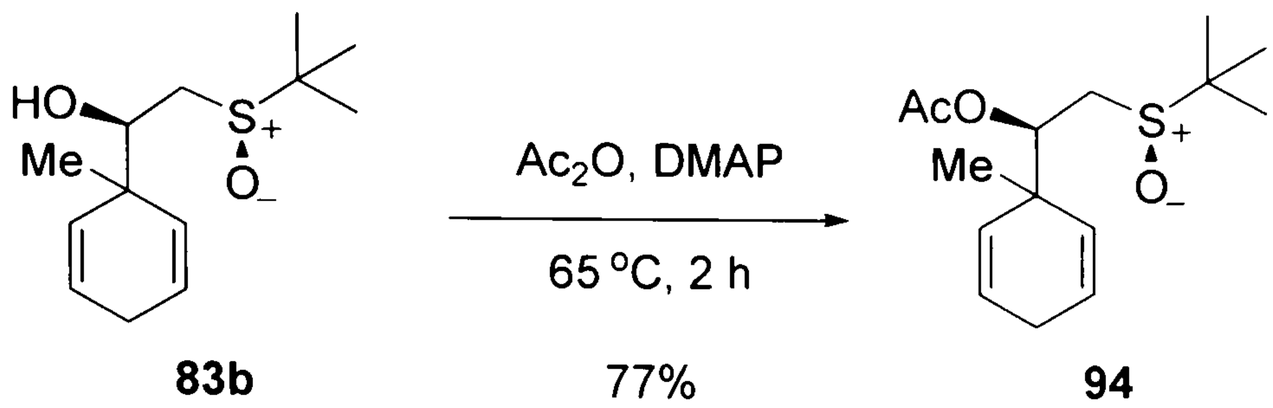


83b **93**

Scheme 45

Sulfoxide **83b** was left for 2 hours to react with the base sodium hydride at 0 °C before benzyl bromide was added to the solution. The product of the reaction was then purified by column chromatography (9:1 diethyl ether/60-80 °C petroleum ether) to afford the benzyl ether **93** as a white solid in good yield. The novel sulfoxide was characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry, IR spectroscopy and melting point analysis.

The free hydroxyl group in **83b** was next acylated with acetic anhydride (Scheme 46).[53]

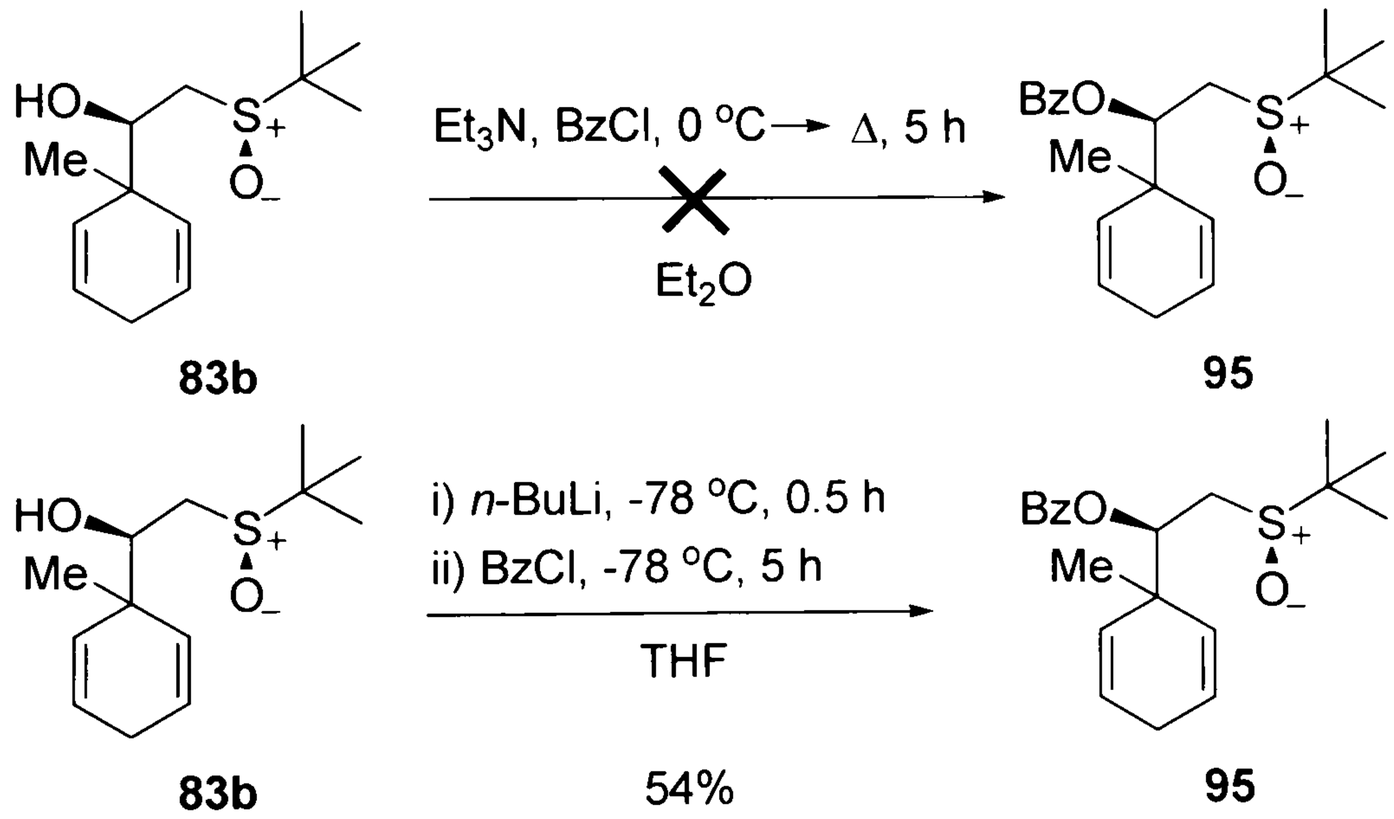


83b **94**

Scheme 46

The sulfoxide **83b** was stirred with acetic anhydride and a catalytic amount of 4-(dimethylamino)-pyridine at 65 °C for two hours to afford the crude product of **94**. which was purified by column chromatography (diethyl ether). The resulting pure compound was obtained as a colourless oil in good yield and was fully characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry and IR spectroscopy.

The alcohol **83b** was esterified with benzoyl chloride (Scheme 47).



83b **95**

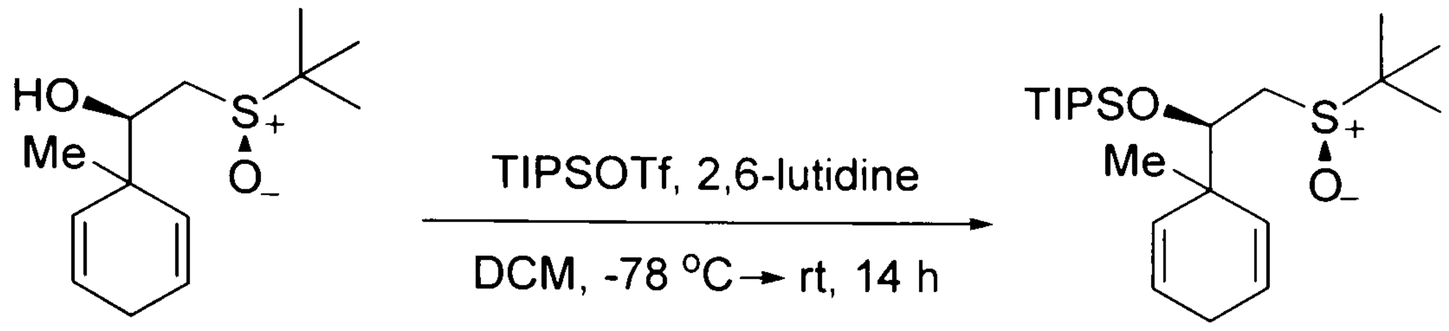
83b **95**

Scheme 47

Attempted protection of alcohol **83b** under standard conditions with triethylamine and benzoyl chloride failed.[54] Alternative reaction conditions proved successful.[55] ß-Hydroxy sulfoxide **83b** was left to react with *n*-butyllithium at -78 °C for 0.5 hours before adding the electrophile benzoyl chloride. The reaction afforded a crude compound which was purified by column chromatography (diethyl ether) to give the protected alcohol **95** as a

white solid in modest yield. The ester was fully characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry, IR spectroscopy and melting point analysis.

The alcohol **83b** was finally protected as a series of silyl ethers (Schemes 48 and 49).

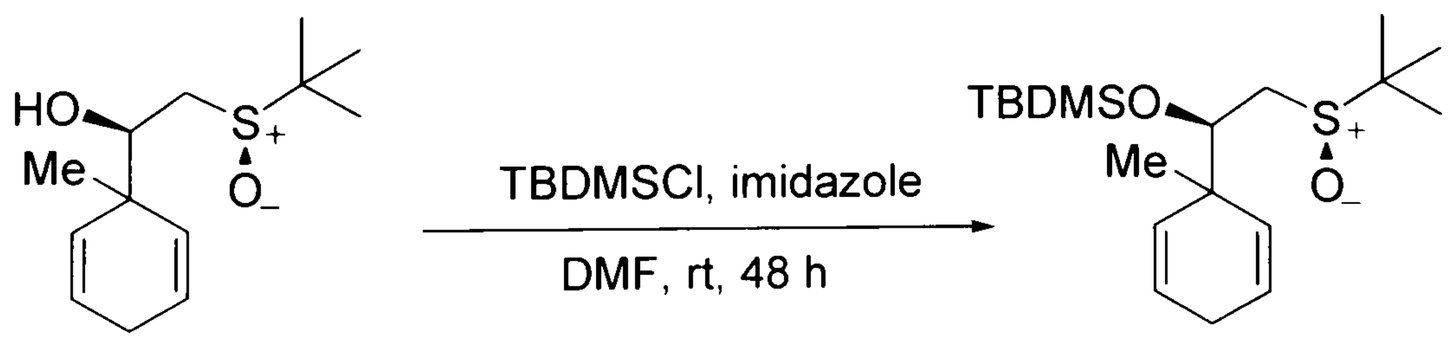


83b 56% **96**

Scheme 48

The alcohol **83b** was reacted with triisopropylsilyl trifluoromethanesulfonate and 2,6-lutidine at -78 °C before the reaction was allowed to warm to room temperature and stirred for 14 hours.[56] The crude compound was purified by column chromatography (4:6 diethyl ether/60-80 °C petroleum ether) to give the pure sulfoxide **96** as a colourless oil in respectable yield. The novel silyl ether **96** was characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry and IR spectroscopy.

The free hydroxyl group was next functionalised with *t*-butyldimethylsilyl chloride to an alternative silyl ether (Scheme 49).[57]



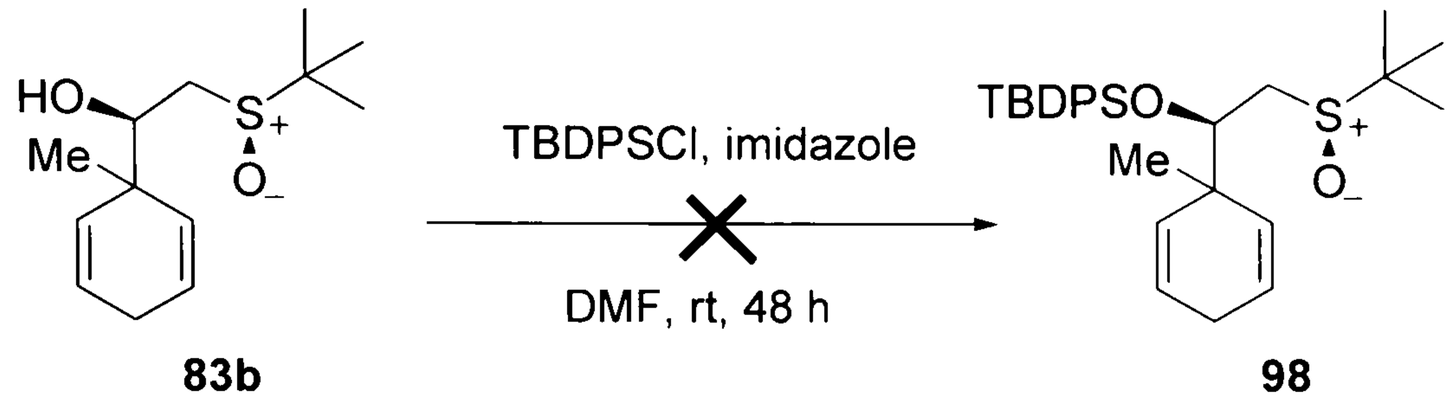
83b 49% **97**

Scheme 49

Alcohol **83b** was stirred with *t*-butyldimethylsilyl chloride and imidazole for 2 days. The reaction mixture was then purified by column chromatography (5:5 diethyl ether/

60-80 °C petroleum ether) to afford 47% of analytically pure sulfoxide **97** and 49% of recovered starting material **83b**. The product was isolated as a colourless oil which was fully characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry and IR spectroscopy.

Attempts to further protect the free hydroxyl functionality as a *t*-butyldiphenylsilyl ether resulted in the isolation of unreacted starting material **83b** (Scheme 50).

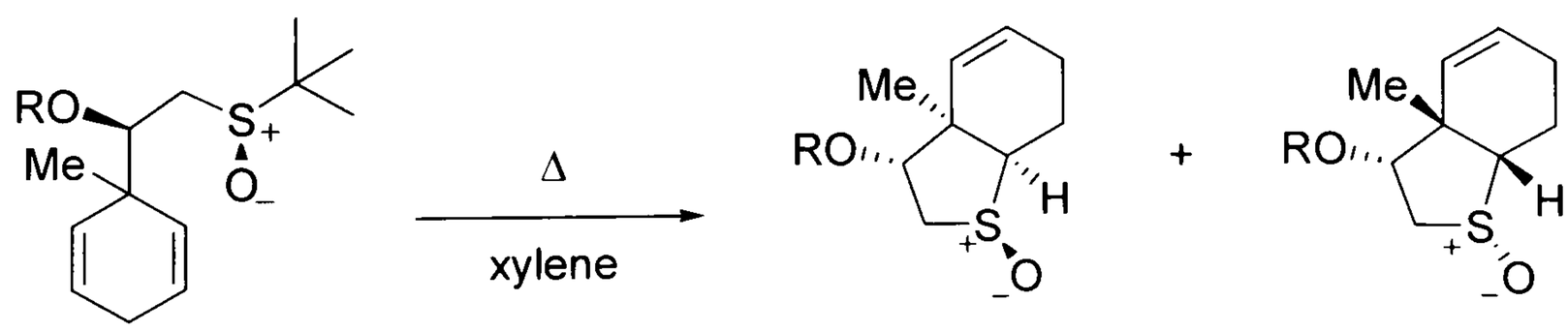


83b **98**

Scheme 50

Possibly this may be attributed to the fact that the secondary alcohol in **83b** with an adjacent quaternary centre suffers from steric encumberance and is therefore unable to react with the bulky electrophile, *t*-butyldiphenylsilyl chloride, as the modest yield for the synthesis of **97** would suggest.

The protected alcohols **92**, **93**, **94**, **95**, **96** and **97** were then independently subjected to the thermolysis conditions as shown in Scheme 51 and the results are summarised in Table 2.



83b,92-97 **91-97a** **91-97b**

Scheme 51

Entry	Substrate	Time/h	Yield(%) [a]	Ratio **a** : **b**
1	R=H, **83b**	3.5	41 [b]	1 : 1 [c]
2	R=Me, **92**	3	65	4 :1 [d]
3	R=Bn, **93**	1	83	3.6 : 1 [d]
4	R=Ac, **94**	4	80	2 : 1 [c]
5	R=Bz, **95**	2.5	74	2 : 1 [d]
6	R=TIPS, **96**	2	45	4.3 : 1 [d]
7	R=TBDMS, **97**	2.5	59	4.9 : 1 [c]

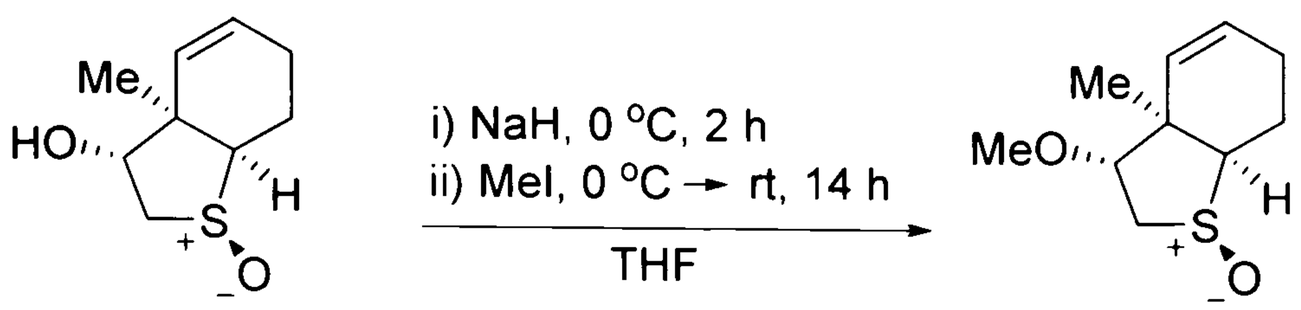
[a] Combined isolated yield of **a** and **b**. [b] 14% recovered starting material **83b**. [c] Ratio of separated cycloadducts. [d] Ratio determined by integration in ^{1}H NMR of combined cycloadducts.

Table 2

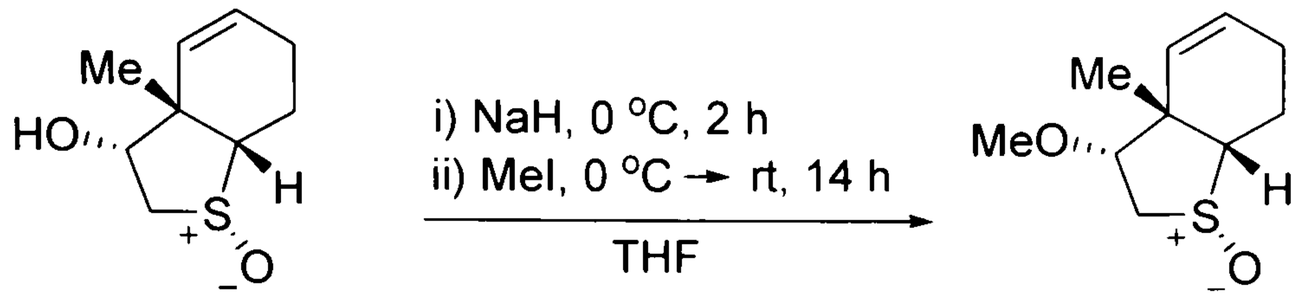
The new cyclic sulfoxides were fully characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry, IR spectroscopy, and melting point analysis, where appropriate.

In each case the stereochemistry of the major and minor products was determined by comparison with alcohols **91a** and **91b**, whose configurations were unambiguously determined by X-ray crystallographic analysis (Figure 6 and Appendices 6.1 and 6.2).

To prove the relative stereochemistry for **92a** and **b**, compound **91a** was subjected to *O*-alkylation with methyl iodide (Scheme 52).



91a 22% **92a**

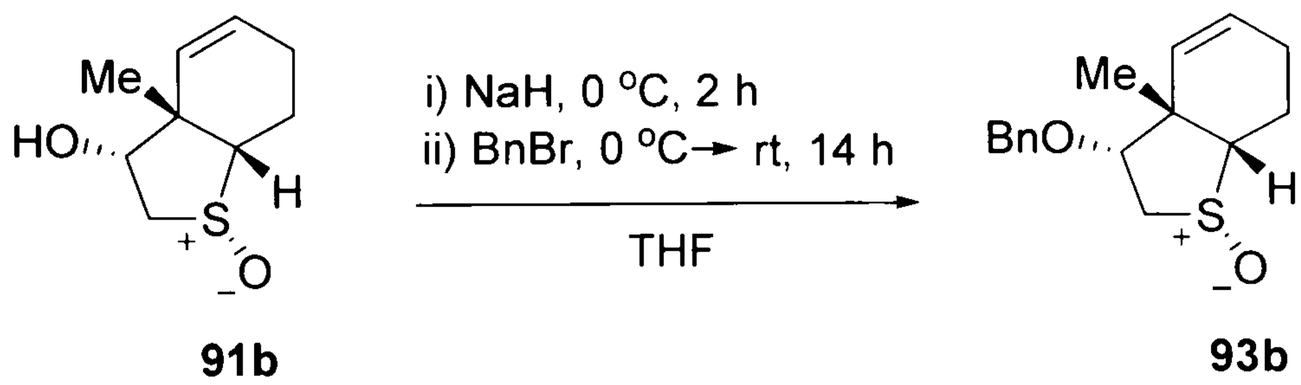


91b 35% **92b**

Scheme 52

Comparison of the ^{1}H NMR spectrum of the product with the ^{1}H NMR spectra of **92a** and **92b** allowed for the identification of the major product of the cyclisation as **92a**. The same technique was used to assign the stereochemistry of **92b**.

The same technique was applied for the assignment of stereochemistry of **93a** and **93b**, as shown in Scheme 53.

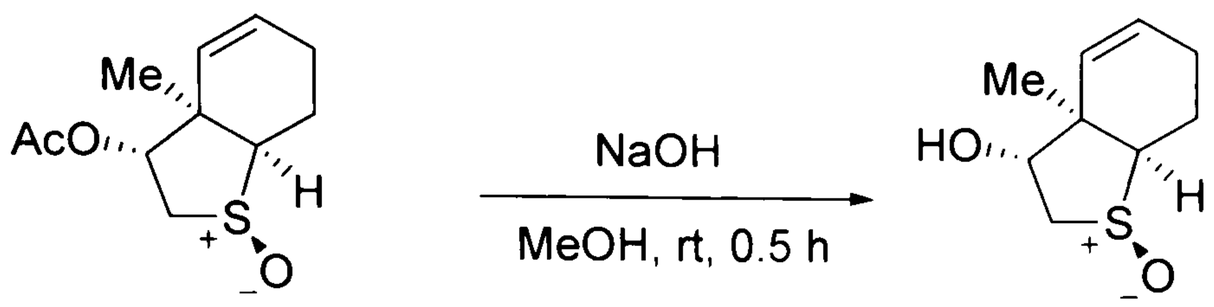


91b **93b**

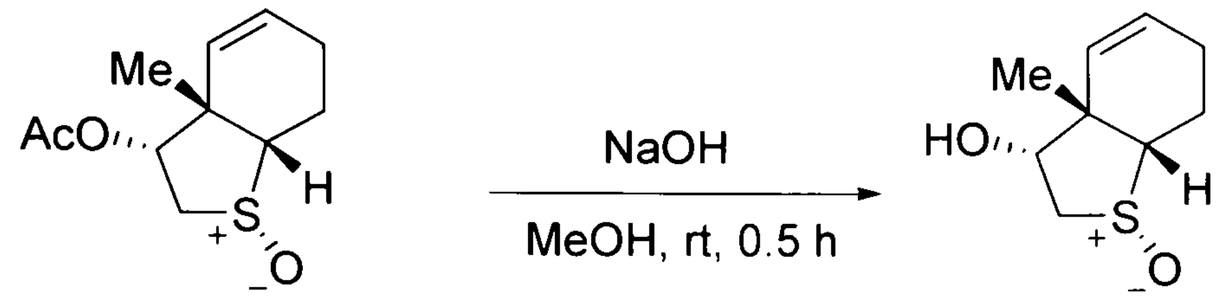
Scheme 53

The assignment was based on ^{1}H NMR spectra analysis. As a result, the configuration of **93a** was also assigned.

For the esters **94-95a** and **94-95b**, basic hydrolysis afforded the corresponding free alcohols of known configuration (Schemes 54 and 55).[58]



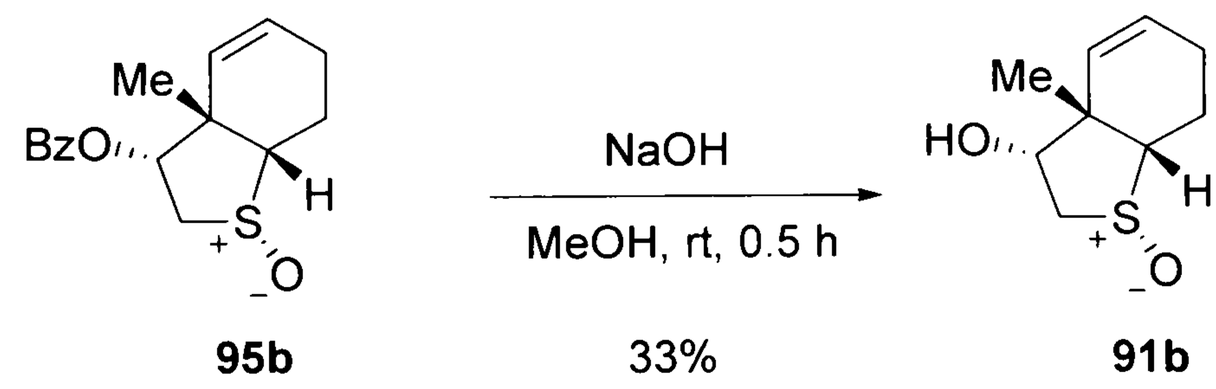
94a 38% **91a**



94b 41% **91b**

Scheme 54

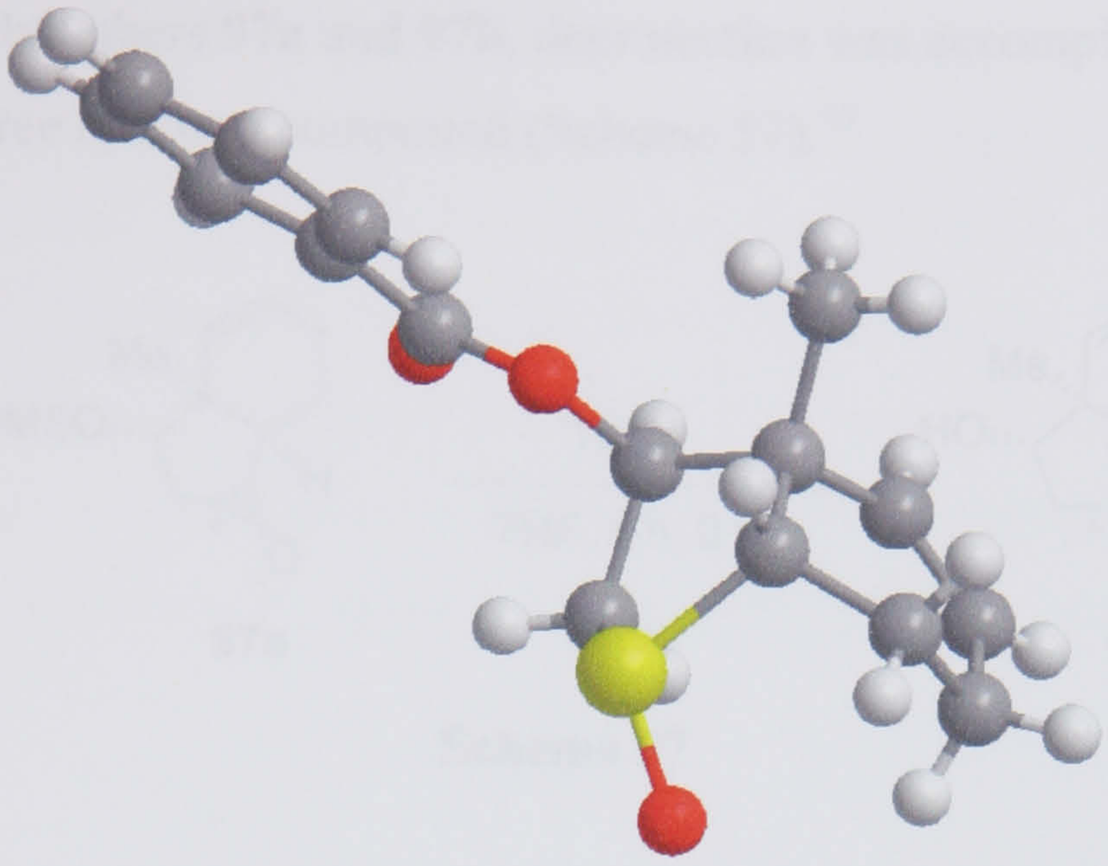
The sulfoxide **94a** was stirred for 0.5 hours with sodium hydroxide in methanol at room temperature. The reaction resulted in a single product that, by comparison with ^{1}H NMR spectra of **91a**, could therefore be identified with the cyclic sulfoxide **91a** possessing *cis* relative stereochemistry between the alcohol and the groups at the bridgehead. As expected hydrolysis of **94b** afforded a compound which corresponded to diastereoisomer **91b**, by ^{1}H NMR analysis.



95b 33% **91b**

Scheme 55

The ^{1}H NMR spectra of the free alcohol derived from **95b** corresponded to that of diastereoisomer **91b**. Furthermore crystallographic analysis for **95a** made the relative stereochemistry unambiguous (Figure 7 and Appendix 6.3).

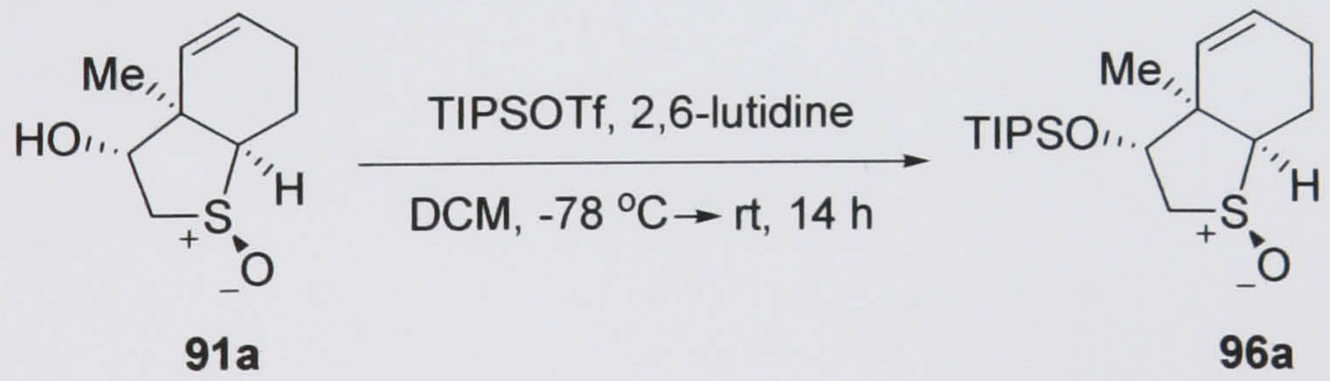


95a

Figure 7

In the crystal structure, the sulfoxide oxygen and bridgehead methyl groups occupy pseudo-equatorial positions on the thiolane ring, and the protected alcohol a pseudo-axial position.

For silyl ethers **96a** and **96b**, compound **91a** was subjected to *O*-silylation as shown in Scheme 56.

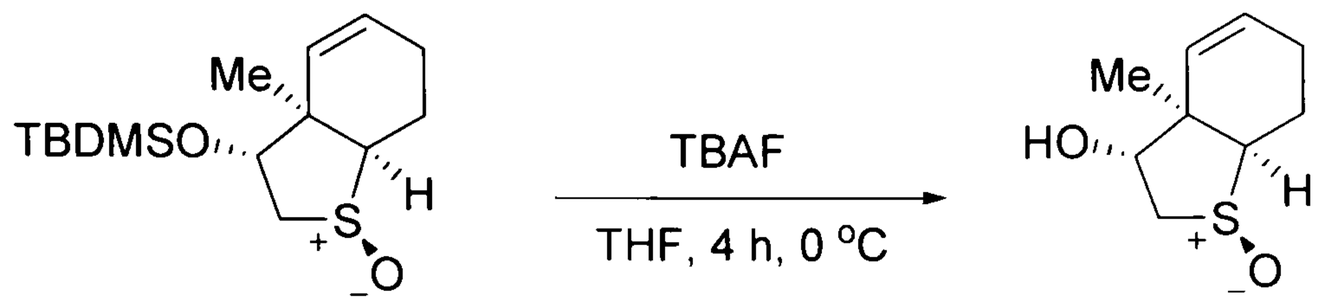


91a **96a**

Scheme 56

The reaction resulted in a single product that, by comparison with ^{1}H NMR spectra of **96a** and **96b**, could therefore be identified with the major diastereoisomer **96a**. The configuration of **96b** was therefore assigned.

In the case of the silyl ethers **97a** and **97b**, deprotection was accomplished with TBAF to the corresponding free hydroxy compound (Scheme 57).[59]



97a 30% **91a**

Scheme 57

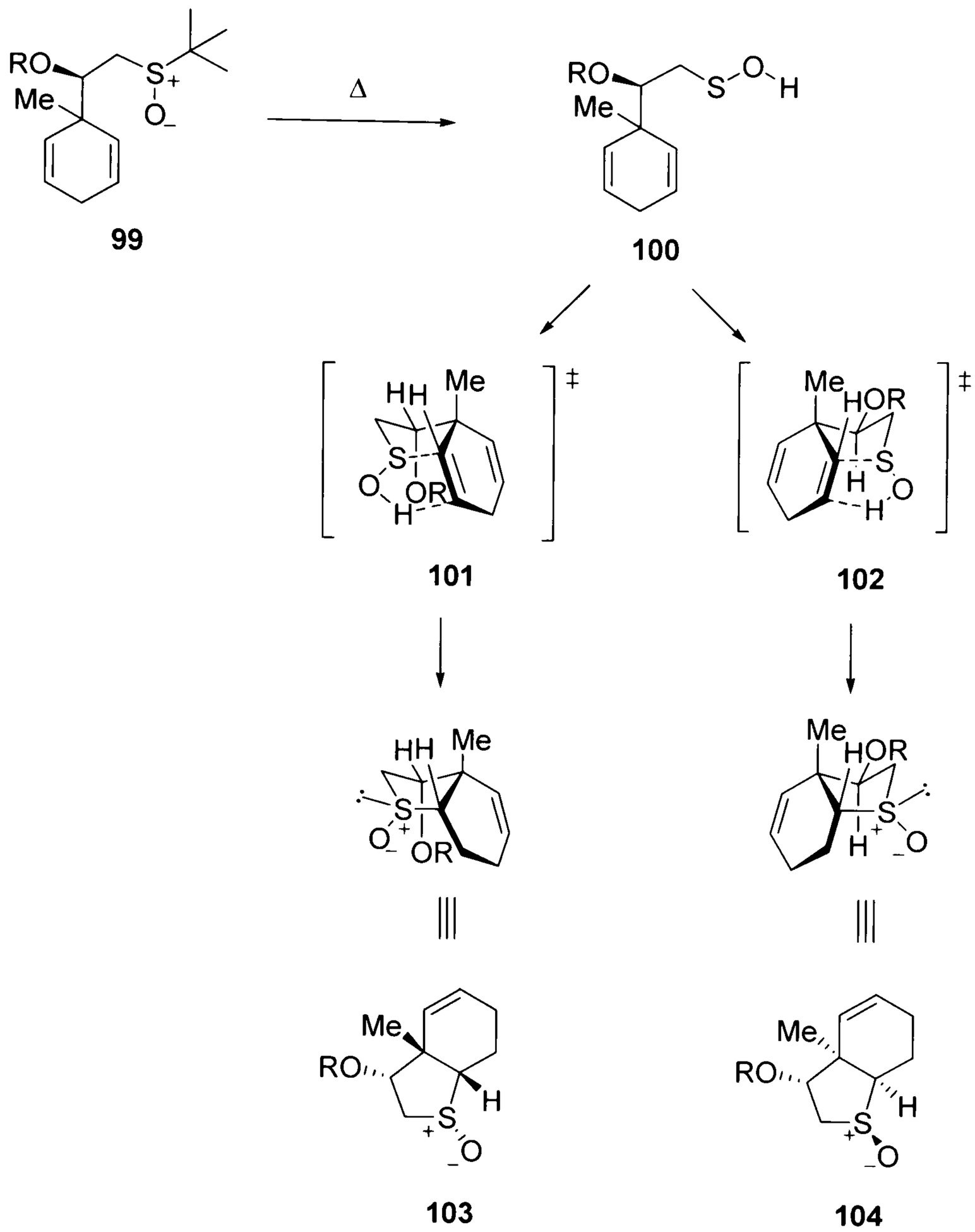
Cleavage of the oxygen-silicon bond of **97a** with tetrabutylammonium fluoride afforded an alcohol which could be assigned, by analysis of the corresponding ^{1}H NMR spectra, as compound **91a**, with the relative stereochemistry as shown. Consequently, the configuration of **97b** was assigned.

Section 2.4: Rationale for the selectivity of the cyclisation

In all cases thermolysis gave rise to a major isomer **91-97a** with the bridgehead methyl and adjacent substituted oxygen *cis* to one another (Table 2, Section 2.3). Alkyl substituents **92** and **93** gave rise to similar levels of selectivity. Lower and identical selectivities were observed for compounds **94** and **95** protected with ester groups. Finally, the optimum selectivity was observed in the case of a silyl ether, with the TBDMS group proving optimum in terms of diastereomeric ratio, product stability and ease of separation.[60]

The diastereomeric ratio is believed to be not simply a reflection of the relative size of the group attached to oxygen. The selectivity observed can be contrasted with the conformational energies (*A*-values) calculated for OX [X= H, Me, Ac, Ts, TMS or *t*-Bu] which show little variation with the nature of X for a substituted cyclohexane.[61]

As anticipated, the protected hydroxyl group acted as a stereochemical control element over the cyclisation and favoured one diastereoisomer over the other. This may be due to the energetic difference of the corresponding diastereotopic transition states **101** and **102** (Scheme 58). In one case, the protected hydroxyl group sits in a pseudo-equatorial position which leads to the major diastereoisomer observed **104**, whereas in the other case the protected alcohol occupies a pseudo-axial position and is presumably therefore a more strained system.



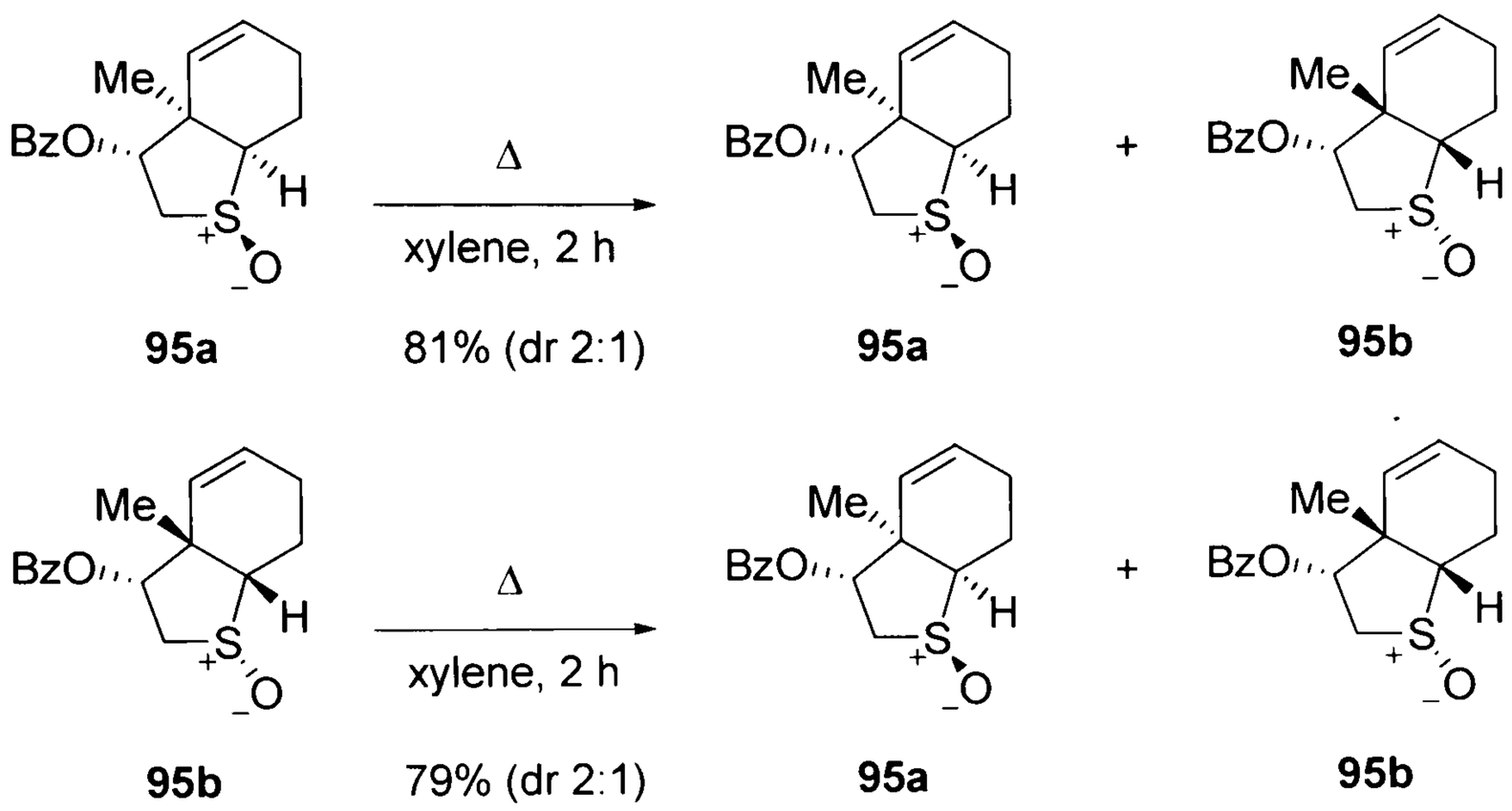
Scheme 58

Hence the observed selectivity could be rationalised in terms of the Hammond postulate,[62] which would imply that diastereoisomer **104** is the kinetic product of the reaction, and therefore the fastest to be formed.

It was therefore felt necessary to carry out a series of experiments to further investigate the nature of the observed selectivity. A known facile test would be to resubmit one of the separated products to the reaction conditions, to see if a mixture or a single product

results. This would permit clarification of the nature of the observed major diastereoisomer, whether it is the thermodynamic or the kinetic product.

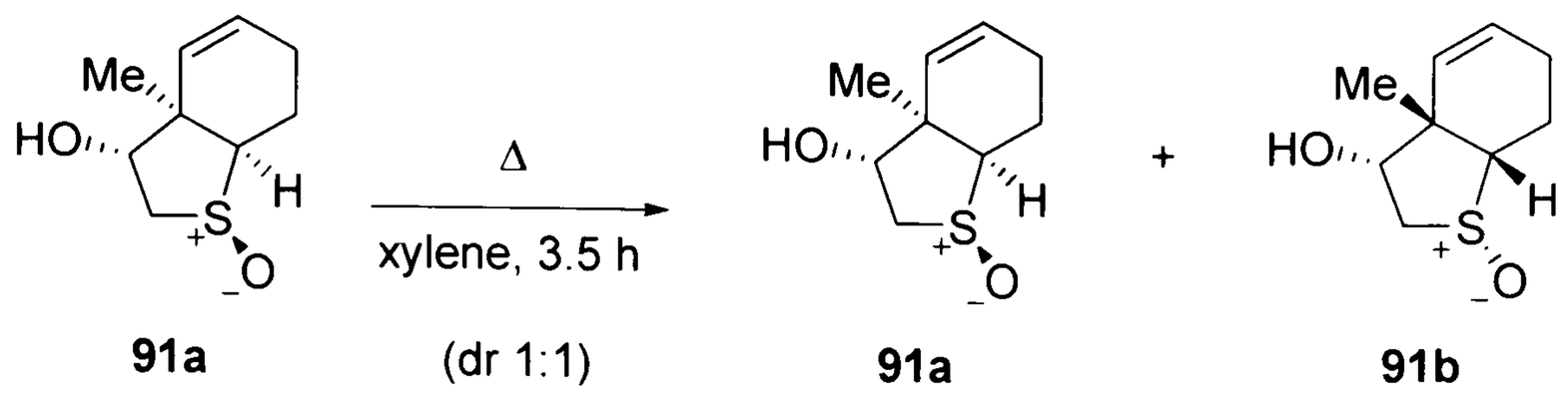
A number of separated sulfoxides were therefore independently re-subjected to the reaction conditions (refluxing xylene) in order to determine the nature of the selectivity in the cyclisation reaction, as shown in Schemes 59 and 60.



Scheme 59

In the case of **95a**, after 2 hours, a mixture of cyclic sulfoxides **95a** and **95b** was observed by thin layer chromatography. After purification by column chromatography (diethyl ether), it was found that the diastereoisomers **95a** and **95b** were present in an identical ratio to that reported for the cyclisation of the linear sulfoxide **95**. A similar result is observed if the other diastereoisomer **95b** is subjected to the identical reaction conditions.

This test has been carried on a number of isolated cyclic sulfoxides, with unprotected and protected alcohol functionalities (Scheme 60).



91a **91a** **91b**

92a **92a** **92b**

94a **94a** **94b**

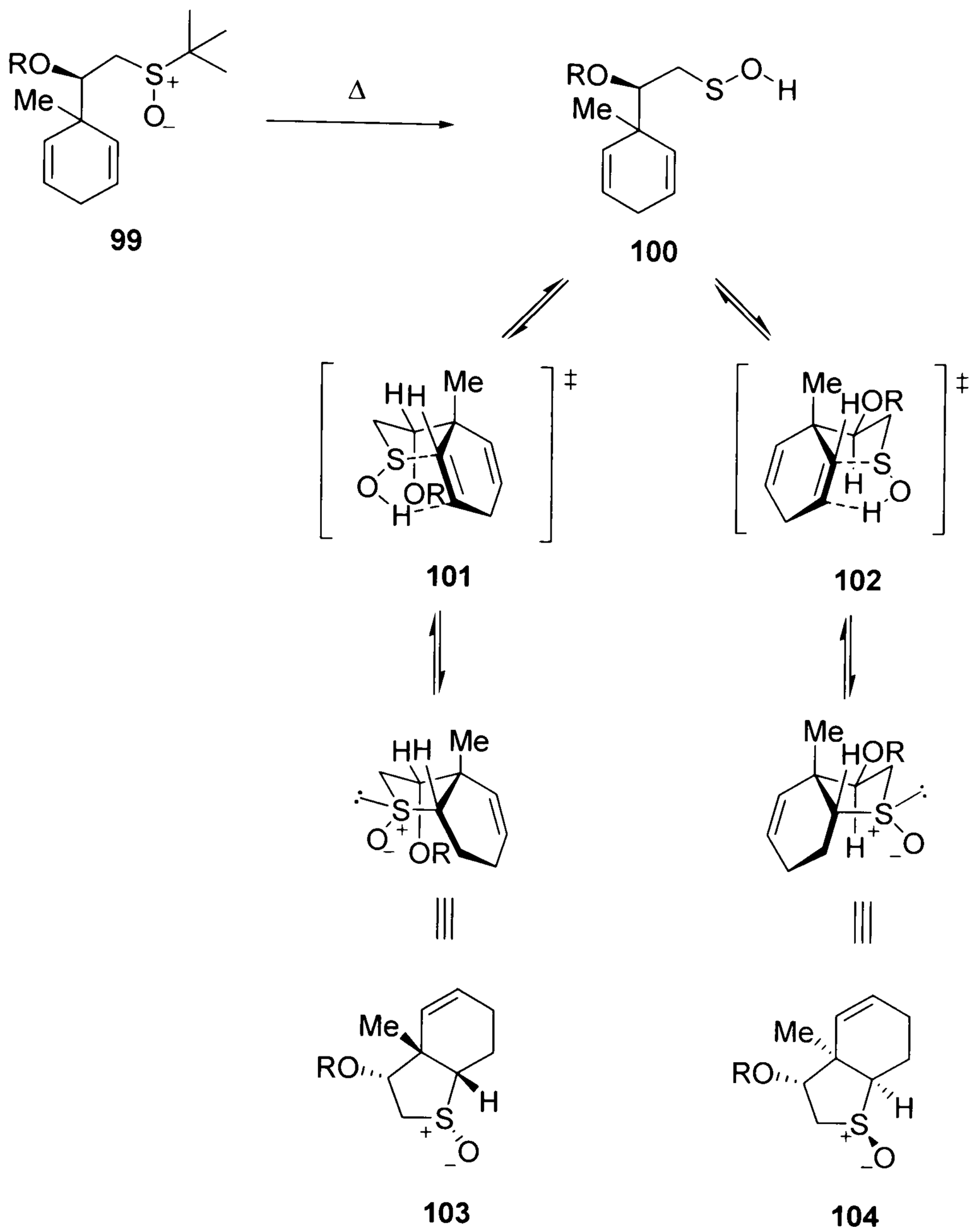
97a 70% (dr 5:1) **97a** **97b**

Scheme 60

In all cases, the resulting mixtures afforded a diastereomeric ratio identical to that observed for the initial cyclisation.

The ratio was calculated on the separated cycloadducts or determined by integration of the respective peaks in the ^{1}H NMR spectra of the combined cycloadducts.

The previous results are consistent with the reaction being under thermodynamic control. The reversible nature of the sulfoxide elimination – sulfenic acid addition reaction means that the product sulfoxides **103** and **104** can also eliminate to reform the sulfenic acid intermediate **100** under the reaction conditions. Presumably the temperature required for the elimination of sulfenic acid from **103** and **104** is similar or less than that required for the elimination of *t*-butyl sulfoxide **99** (Scheme 61).[4]



Scheme 61

Therefore, the resulting major diastereoisomer is believed to be the thermodynamic product. To confirm this analysis, a final proof of concept would be to perform a non-reversible reaction i.e. one under complete kinetic control and check the ratio of cycloadducts. Due to the nature of the reaction, the cyclic sulfoxides **103** and **104** should not be able to interconvert, *via* the formation of the sulfenic acid intermediate **100**. Therefore, for the experiment to succeed, it would require a lower temperature than refluxing xylene to avoid the sulfoxide elimination from substrates **103** and **104** and a method of generating sulfenic acid **100** that does not require similarly high temperatures.

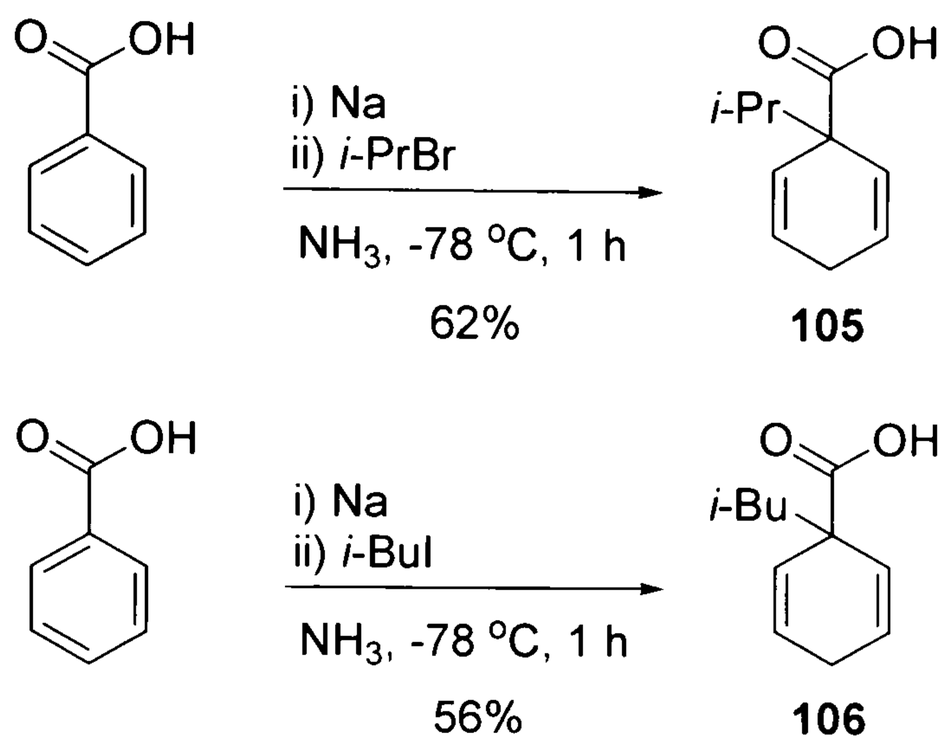
If as the result of these experiments, the major diastereoisomer is still **104**, it would mean that **104** is both the thermodynamic and the kinetic product.

Synthetic studies towards this end are reported in Section 2.5.

Section 2.5: Variation of alkyl substituents at the bridgehead position

To gain further insight into the selectivity of the cycloaddition process, cyclisation precursors with different alkyl groups (*i*-Pr, *i*-Bu, *t*-Bu) at the *ipso* position have been synthesised and tested.

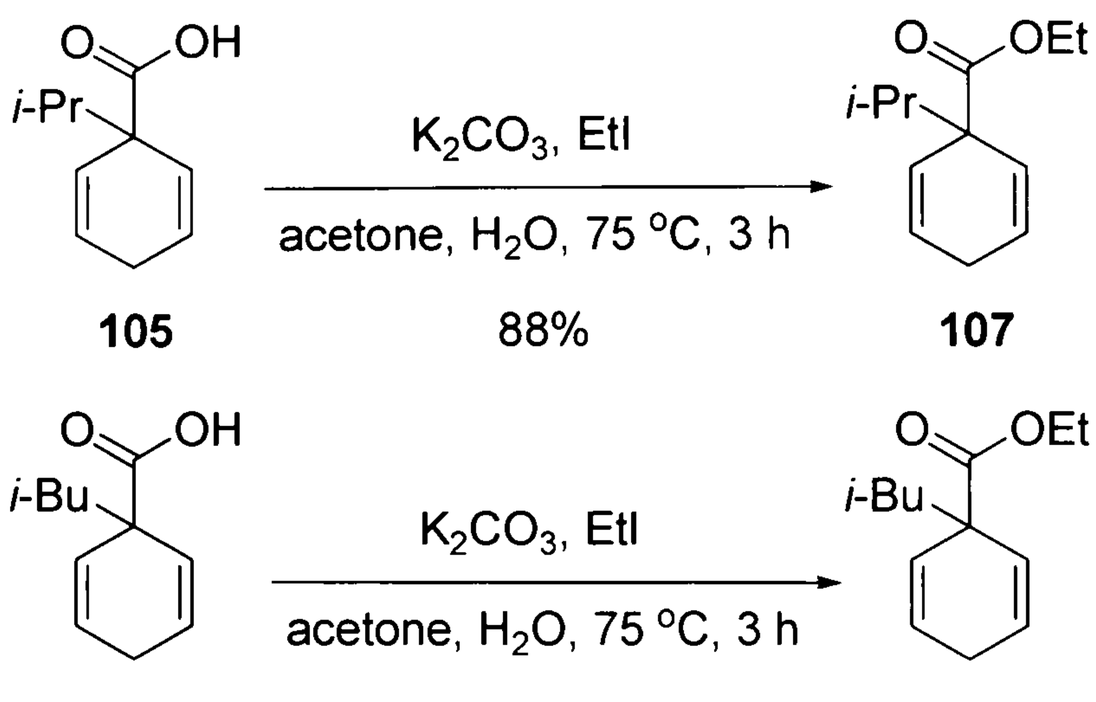
Synthesis of dienes **105** and **106** was accomplished following a reported literature procedure (Scheme 62).[63]



Scheme 62

Benzoic acid was reacted with sodium in condensed ammonia to furnish an anion that was quenched with the electrophiles *i*-propyl bromide and *i*-butyl iodide to give **105** (lit.[63] 71%) and **106** (lit.[63] 61%). The isolated products **105** and **106** were considered pure enough by ^{1}H NMR analysis to be submitted to the next step of the synthesis.

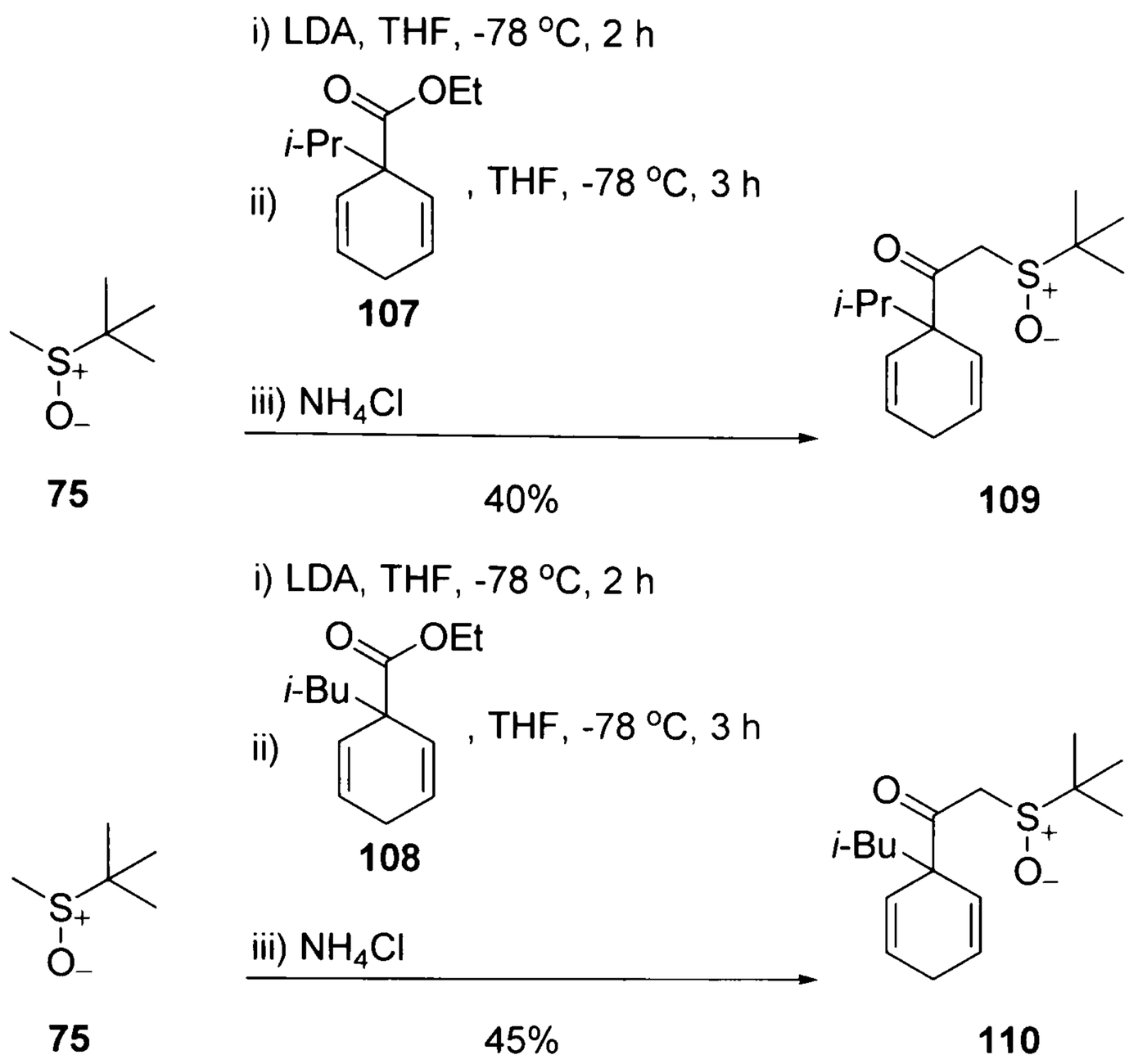
The carboxylic acids were derivatised to the corresponding ethyl esters **107** and **108** respectively (Scheme 63).[64]



Scheme 63

The esters **107** and **108** were formed after 3 hours of heating substrates **105** and **106** with the electrophile ethyl iodide in an acetone-water mixture. The novel compounds **107** and **108** were isolated analytically pure as colourless oils and were characterised by ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry and IR spectroscopy. Compound **107** was not characterisable by mass-spectrometry.

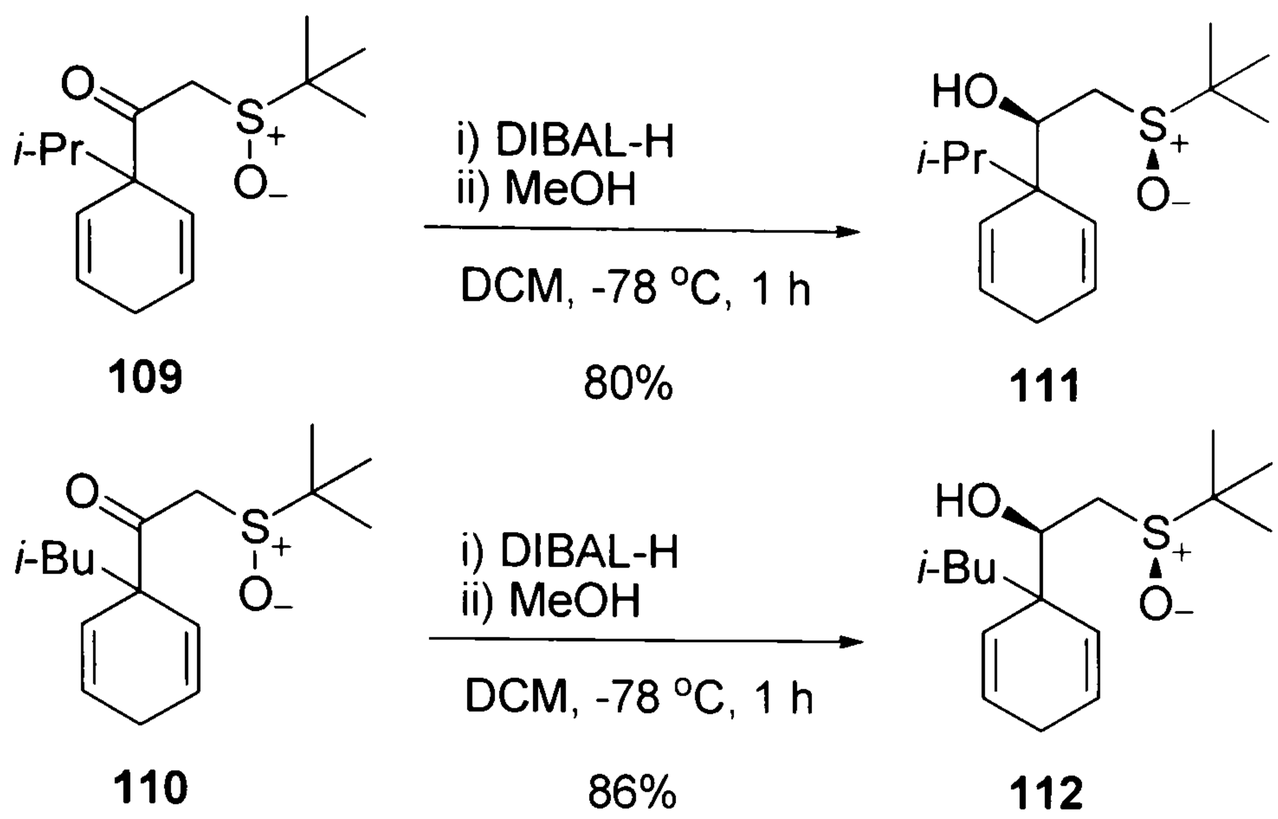
The esters **107** and **108** were then submitted to a condensation reaction to afford the ß-keto sulfoxides **109** and **110** as outlined in Scheme 64.



Scheme 64

The anion of *t*-butyl methyl sulfoxide was stirred for 3 hours with ethyl esters **107** and **108** to afford the crude sulfoxides **109** and **110** respectively. Purification by column chromatography (diethyl ether) resulted in the independent isolation of the novel compounds **109** and **110** as yellow oils in modest yields, whose full characterisation was ascertained by ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry and IR spectroscopy.

The ß-keto sulfoxides **109** and **110** were subjected to chemo- and stereoselective reduction with diisobutylaluminum hydride (Scheme 65).



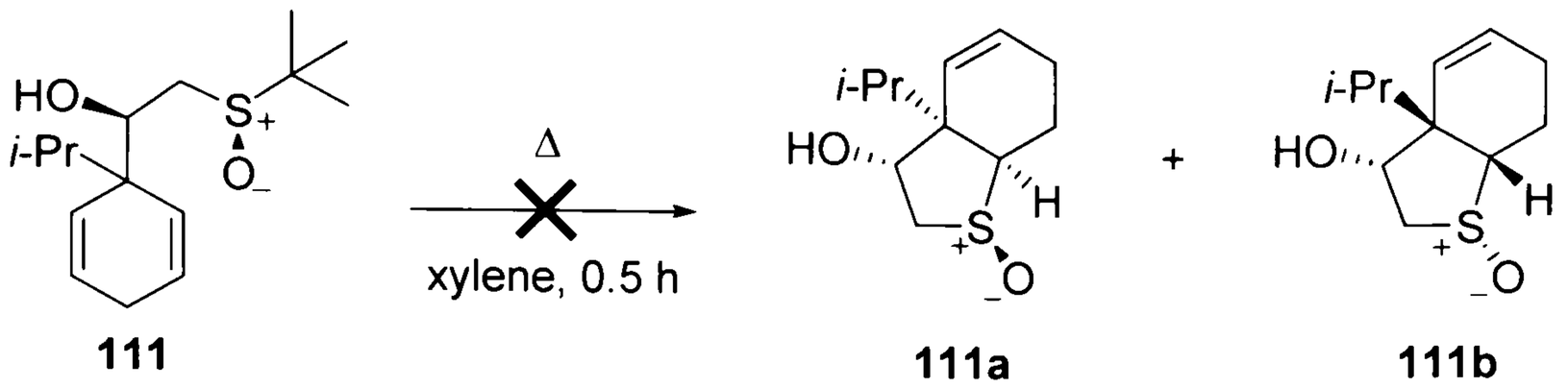
109 **111**

110 **112**

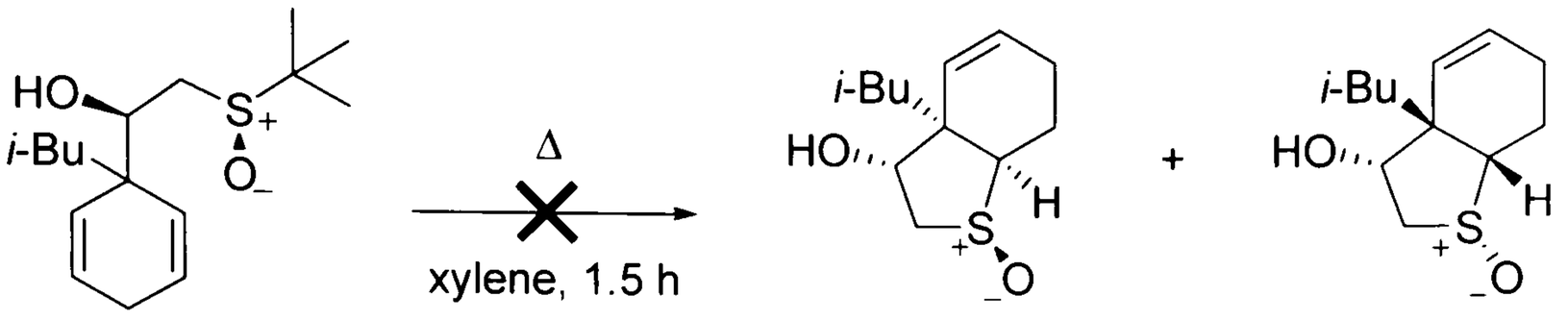
Scheme 65

Substrates **109** and **110** were independently stirred for 1 hour with the reducing agent diisobutylaluminum hydride at -78 °C, before addition of methanol to quench the reaction. The reactions afforded products **111** and **112** respectively as white solids which required no further purification after a standard work-up procedure. The relative stereochemistry between the alcohol and the sulfoxide was assumed to be *trans*, following the Solladié model.[47] The novel compounds were fully characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry, IR spectroscopy and melting point analysis.

Attempts to affect the cyclisation of substrate **111** failed due to decomposition of the starting material under the reaction conditions (Scheme 66).



111 **111a** **111b**

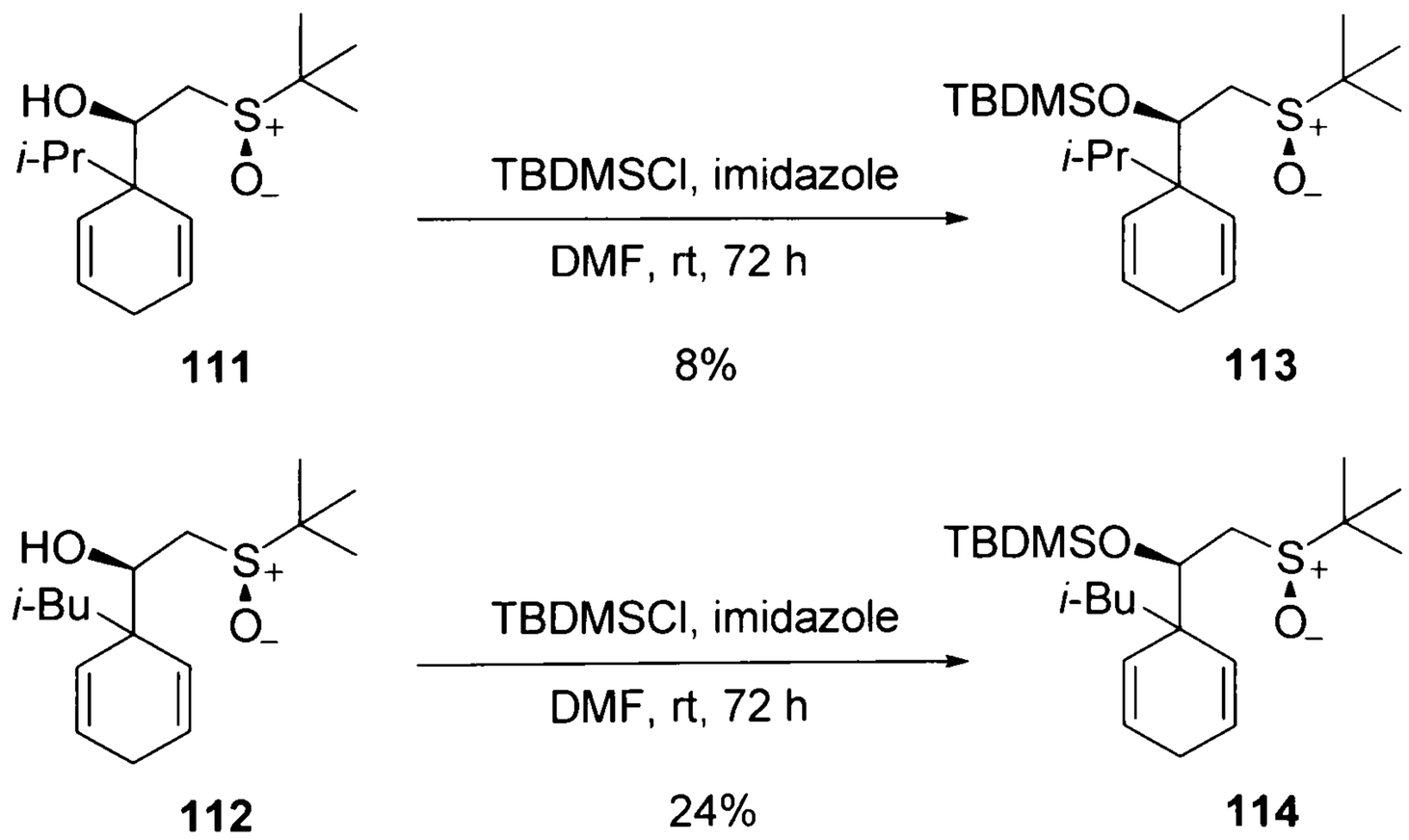


112 **112a** **112b**

Scheme 66

A similar result was encountered in the attempted cyclisation of alcohol **112**.

The alcohols **111** and **112** were next protected as *t*-butyldimethylsilyl ethers (Scheme 67), as this protecting group gave the best selectivity for the substrate with methyl at the *ipso* position (Table 2, Section 2.3).



111 **113**

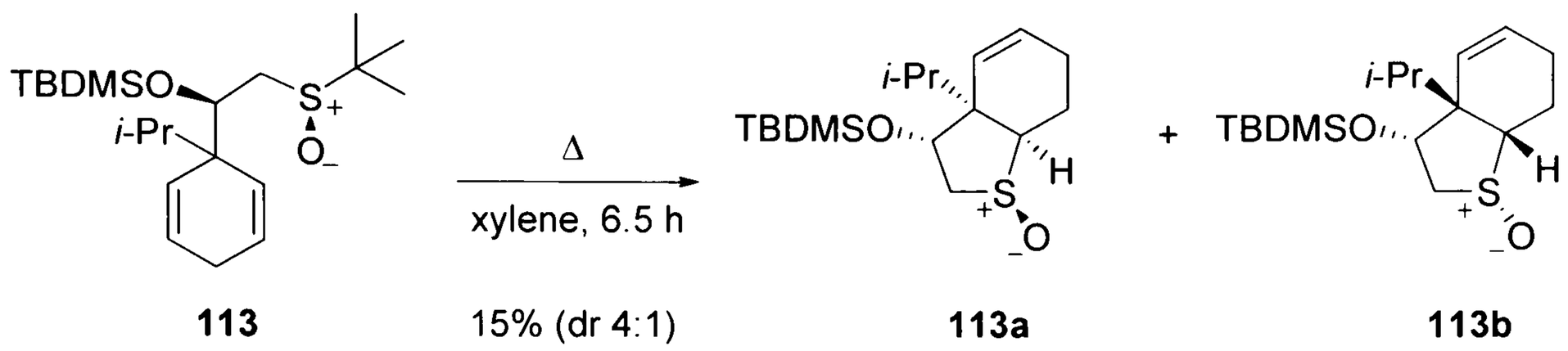
112 **114**

Scheme 67

The alcohols **111** and **112** were independently stirred in anhydrous *N,N*-dimethylformamide with *t*-butyldimethylsilyl chloride and imidazole at room temperature for three days. After purification by column chromatography (diethyl ether) compounds

113 and **114** were isolated as white solids in very poor yield. The low yield of the protection might be attributed to the steric encumberance of the position where the electrophile has to react. The novel compounds were fully characterised by ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry, IR spectroscopy and melting point analysis.

The novel sulfoxide **113** was submitted to the standard thermolysis conditions, as depicted in Scheme 68.

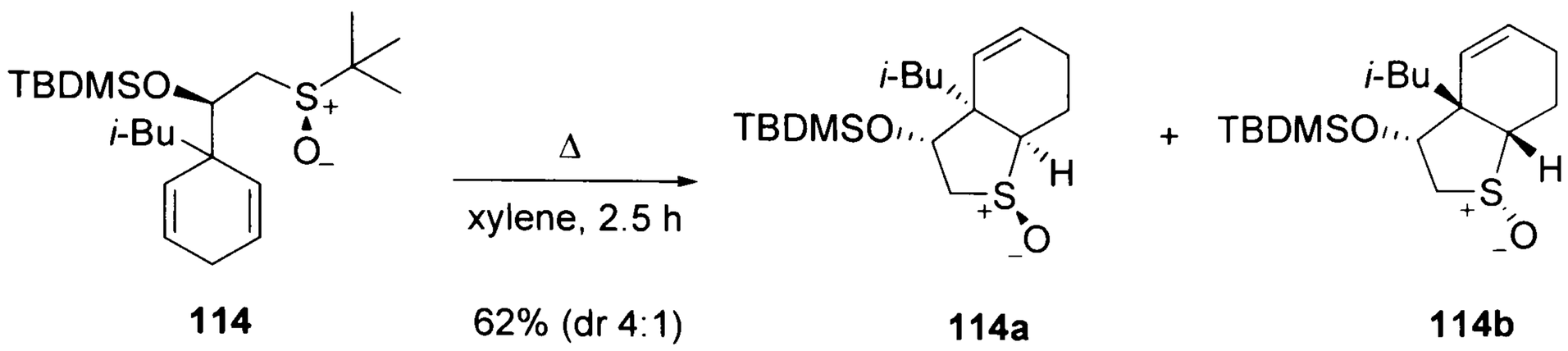


113 15% (dr 4:1) **113a** **113b**

Scheme 68

After 6.5 hours of refluxing in xylene, the reaction mixture was subjected to column chromatography (6:4 diethyl ether/60-80 °C petroleum ether) to remove the solvent and purify the crude product. The isolated product by analysis of its corresponding ^{1}H NMR spectra appeared to be a mixture of the cyclic sulfoxides **113a** and **113b** in a diastereomeric ratio of 4 to 1. The relative stereochemistry of the major diastereoisomer could not be determined by NOESY experiments. The novel mixture was fully characterised by ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry and IR spectroscopy.

An identical diastereomeric ratio was observed for the cyclisation of silyl ether **114** (Scheme 69).



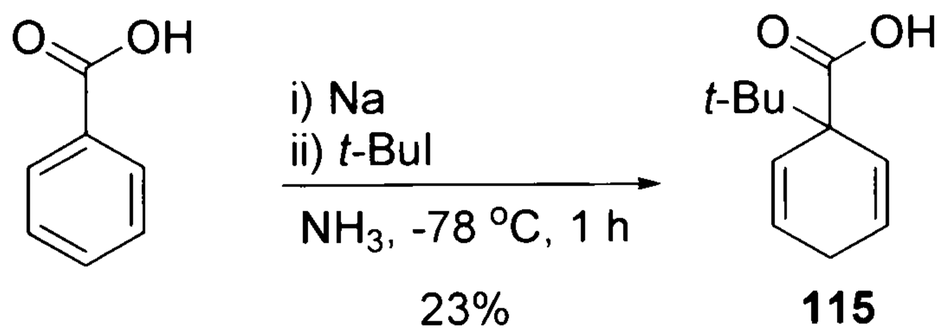
114 62% (dr 4:1) **114a** + **114b**

Scheme 69

Thermolysis of sulfoxide **114** afforded an inseparable mixture of cyclic silyl ethers **114a** and **114b** in a diastereomeric ratio of 4 to 1 by ^{1}H NMR spectroscopy. The stereochemistry of the products could not be determined by NOESY. The novel mixture of cyclic sulfoxides was fully characterised by ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry and IR spectroscopy.

The effect of a *t*-butyl group at the *ipso* position was then investigated.

Conversion of commercially available benzoic acid to the corresponding 1,3-diene **115** was effected following a reported literature procedure and is shown in Scheme 70.[63]

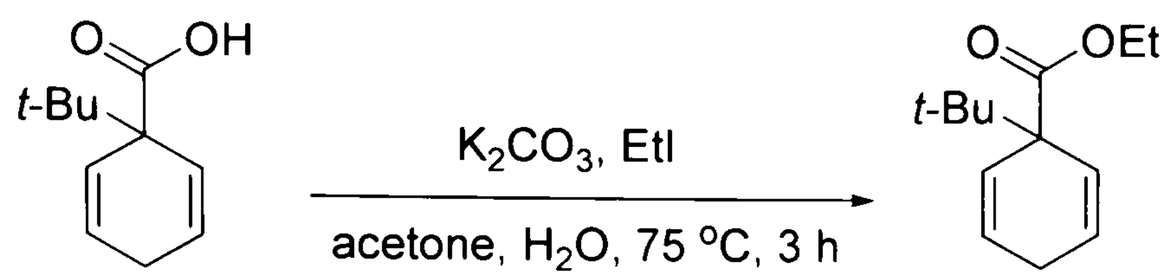


23% **115**

Scheme 70

Benzoic acid was stirred in a condensed solution of ammonia, sodium was then added followed by the electrophile *t*-butyl iodide. The 1,3-diene product **115** was isolated after a standard work-up procedure and was obtained in a low yield, comparable to that reported in the literature (lit.[63] 22%). The carboxylic acid **115** was deemed pure enough to be carried through to the next step of the synthesis, by analysis of its ^{1}H NMR spectra.

The carboxylic acid **115** was next converted to its corresponding ethyl ester (Scheme 71).[64]

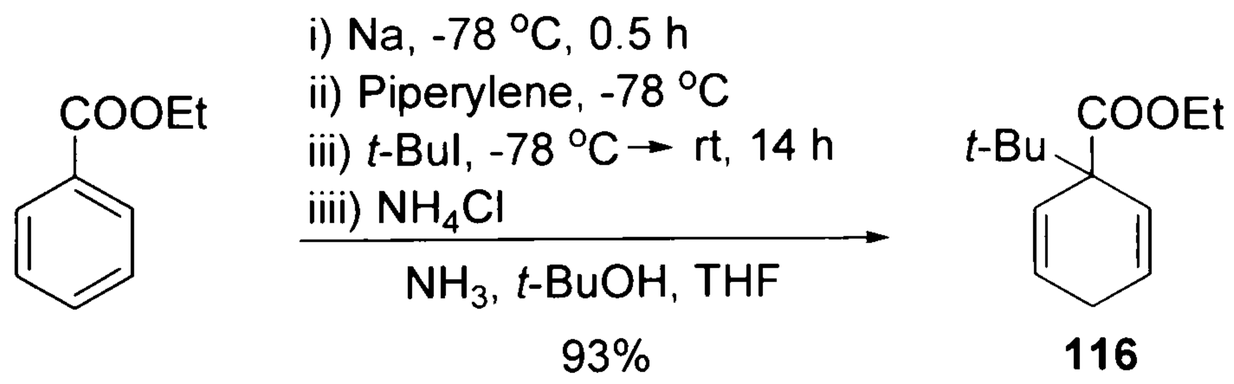


115 94% **116**

Scheme 71

The diene **115** was stirred with potassium carbonate and the electrophile ethyl iodide for three hours and the reaction was monitored to completion by thin layer chromatography. The novel ester **116** was isolated following a standard work-up procedure and was fully characterised by ^{1}H and ^{13}C NMR spectroscopy low and high resolution mass-spectrometry and IR spectroscopy.

Attempts to affect the Birch reduction of ethyl benzoate and quench the resultant anion with *t*-butyl iodide proved an alternative more efficient strategy to the synthesis of **116**. The reaction conditions are outlined in Scheme 72.

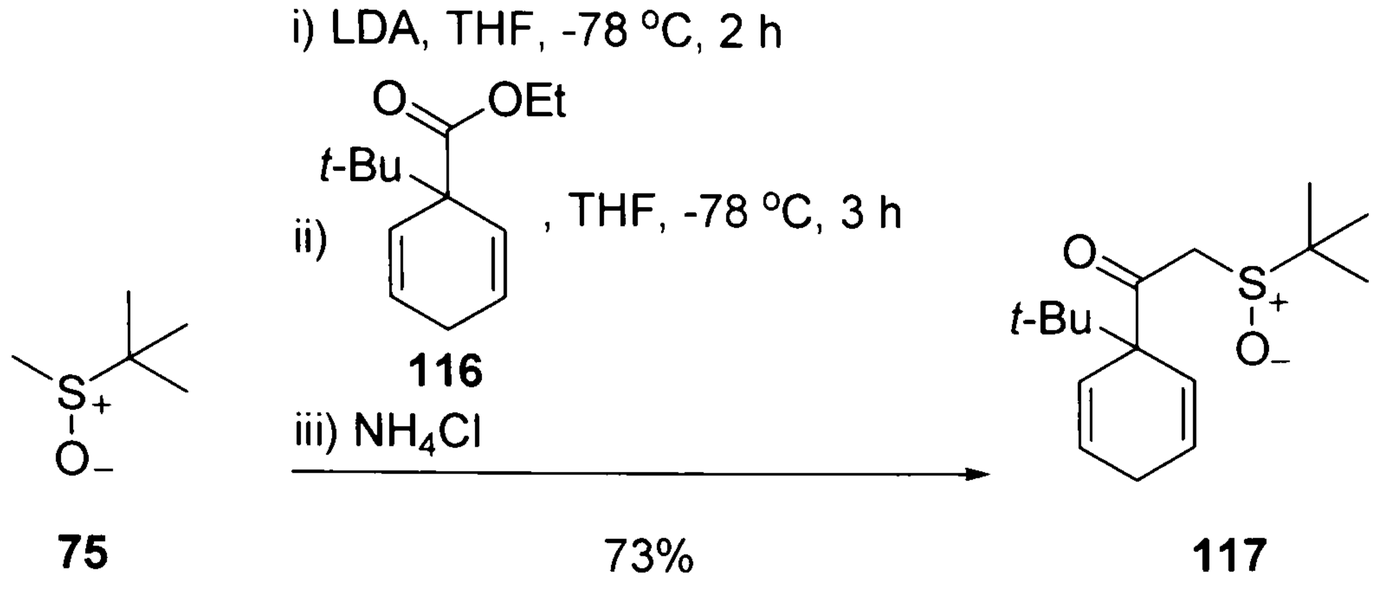


116

Scheme 72

The optimum reaction conditions allowed the electrophile *t*-butyl iodide to react with the Birch reduction product overnight, by which time all the ammonia had evaporated. The reaction afforded the desired compound **116** in an excellent yield without the need for further purification.

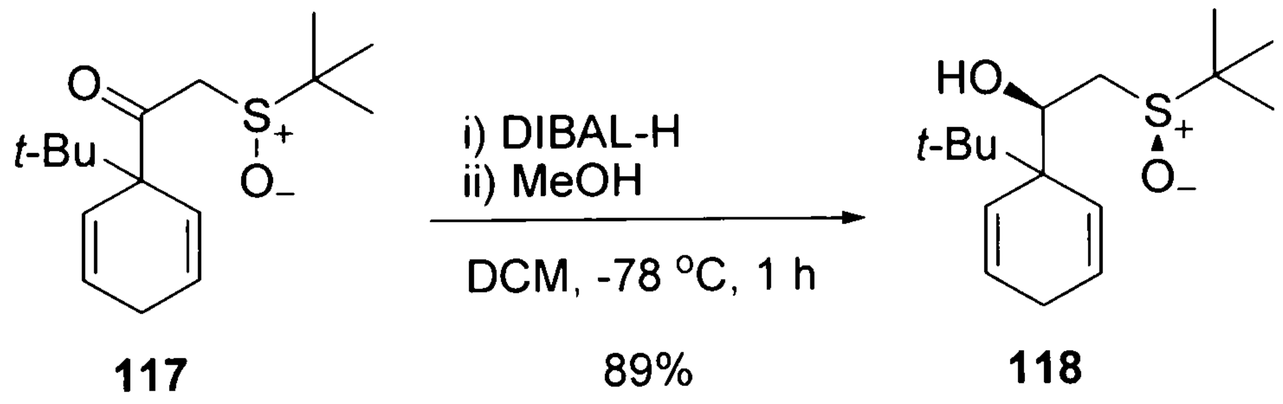
Ethyl ester **116** was then reacted with the anion of *t*-butyl methyl sulfoxide to generate the ß-keto sulfoxide **117** (Scheme 73).



Scheme 73

The anion of *t*-butyl methyl sulfoxide **75** was left to react with ester **116** at -78 °C for three hours. The reaction mixture was then worked-up and the crude product was purified by column chromatography (diethyl ether) to afford the ketone **117** in good yield as a white solid. The novel ester was fully characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry, IR spectroscopy and melting point analysis.

Stereoselective reduction of ketone **117** afforded the desired alcohol **118**, as described in Scheme 74.

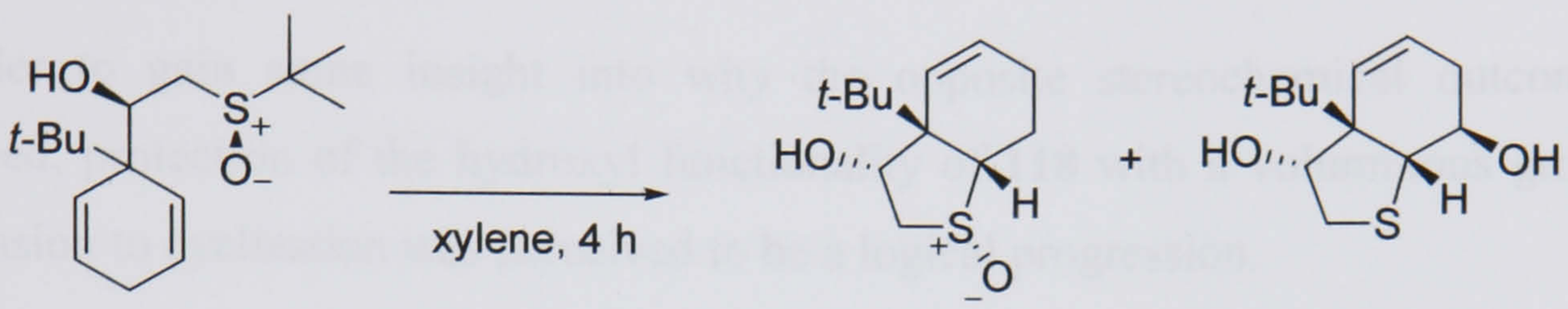


Scheme 74

Sulfoxide **117** was stirred for one hour with the reducing agent diisobutylaluminum hydride before the reaction was quenched with methanol. After work-up, the reaction afforded the product **118** as a white solid in good yield which did not require further purification, as determined by ^{1}H NMR analysis. The stereochemistry is expected to be

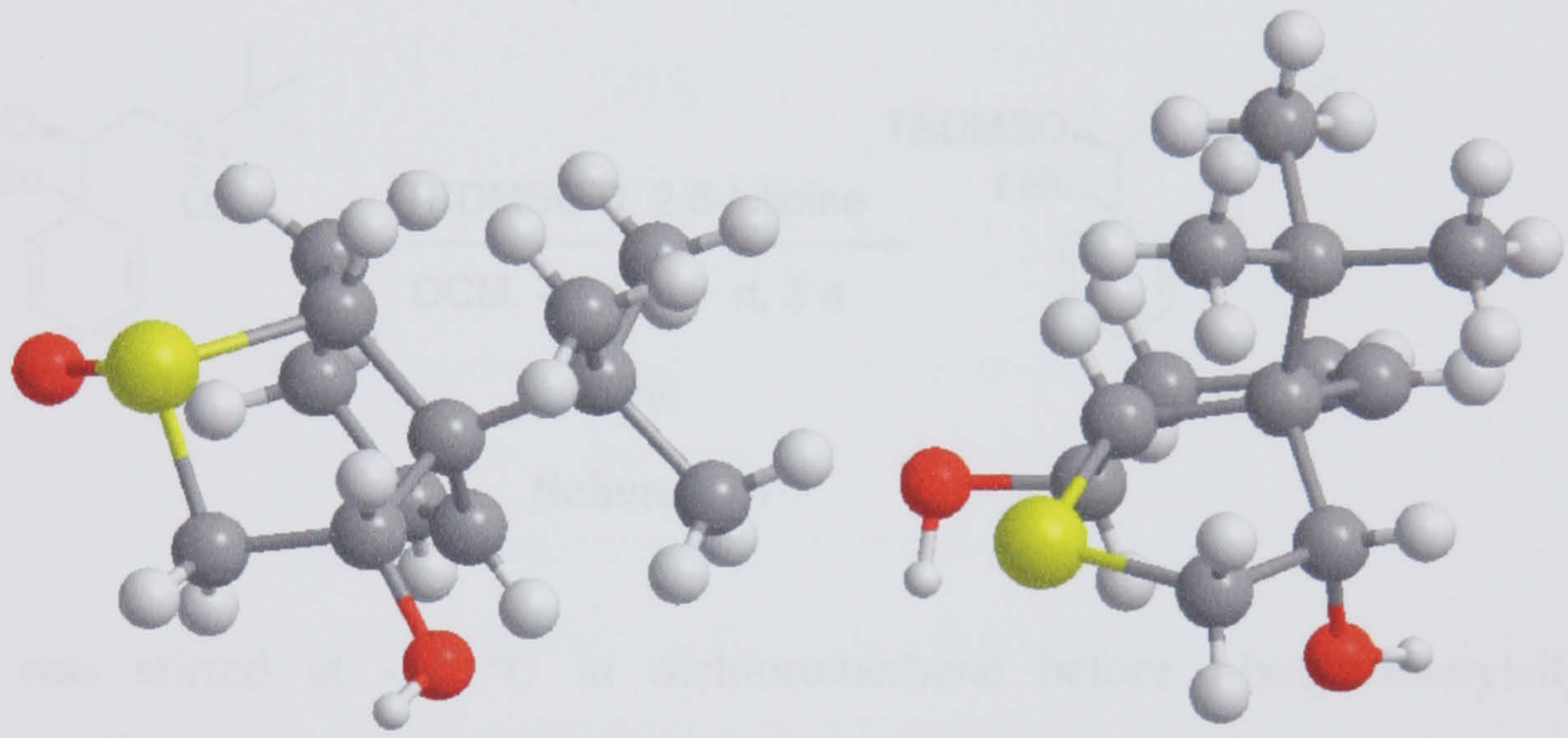
trans to be consistent with the Solladié model.[47] The novel compound was characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry, IR spectroscopy and melting point analysis.

The alcohol **118** was next submitted to the standard thermolysis conditions (Scheme 75).



118 **118a**, 41% **118b**, 2%

Scheme 75



118a **118b**

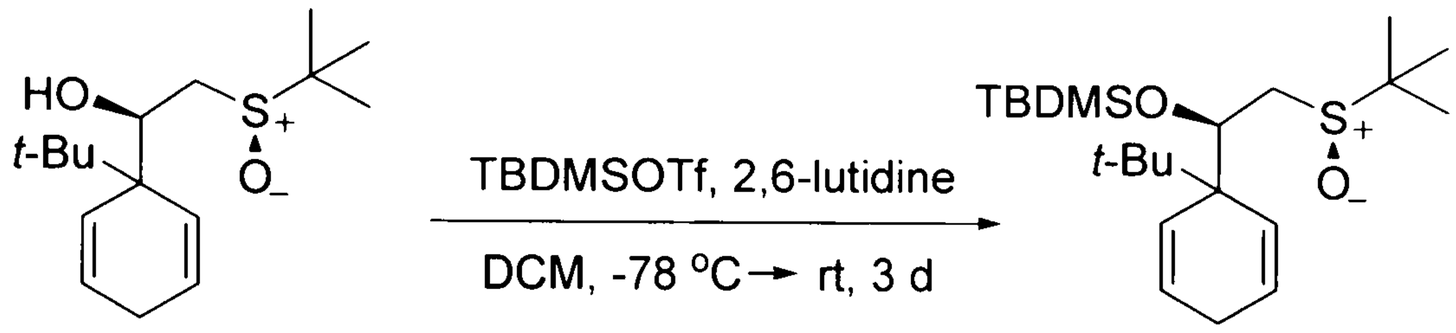
Figure 8

After 4 h of reflux, the reaction revealed two new products by thin layer chromatography and it was decided to stop the reaction and isolate the products by column chromatography (diethyl ether), to avoid unwanted side reactions. This allowed the recovery of 16% of unreacted starting material and the isolation of two new cyclic alcohols, as determined by their respective ^{1}H NMR spectra. The major product **118a**, isolated in 41% yield, is a cyclic sulfoxide, whereas the minor product, ß-dihydroxy sulfide **118b**, was isolated in only 2% yield. The relative stereochemistry of the novel

compounds **118a** and **118b** was unambiguously assigned by X-ray crystallographic analysis (Figure 8 and Appendices 6.4 and 6.5). The origin of cyclic sulfide **118b** is not clear. However, the cyclisation of linear sulfoxide **118** gratifingly afforded only one diastereoisomer **118a**, but with the opposite relative stereochemistry compared to the major cycloadducts **91-97a** (Section 2.3).

In order to gain some insight into why the opposite stereochemical outcome was observed, protection of the hydroxyl functionality of **118** with a voluminous group and submission to cyclisation was perceived to be a logical progression.

The ß-hydroxy sulfoxide **118** was protected as its *t*-butyldimethylsilyl ether (Scheme 76).

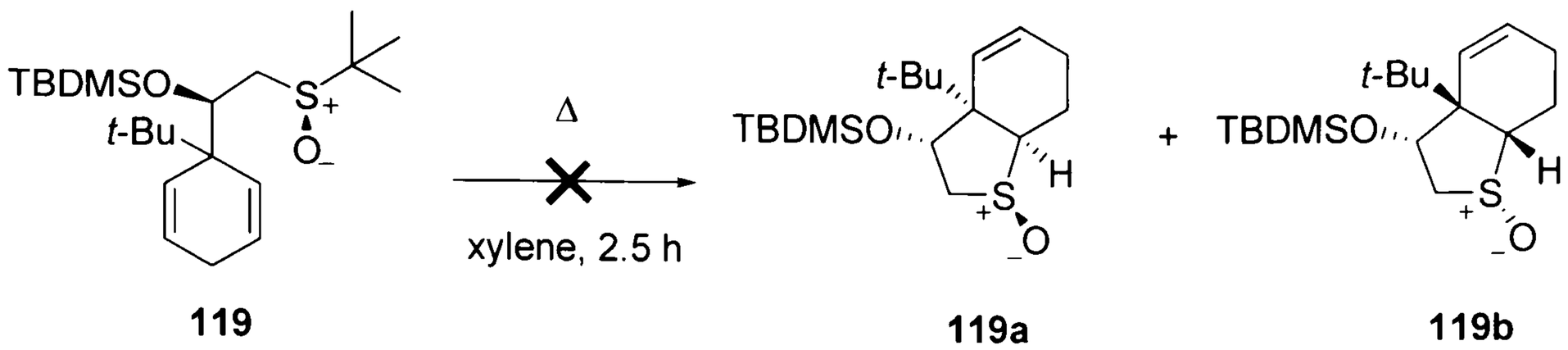


118 32% **119**

Scheme 76

Alcohol **118** was stirred at -78 °C in dichloromethane before *t*-butyldimetylsilyl trifluoromethanesulfonate and 2,6-lutidine were added to the solution and the reaction was allowed to warm to room temperature. After three days of stirring the reaction was worked-up and the crude mixture was purified by column chromatography (7:3 diethyl ether/60-80 °C petroleum ether) to afford the protected alcohol in poor yield. The novel compound was fully characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry and IR spectroscopy. The product was deemed pure enough to be submitted to the standard cyclisation conditions.

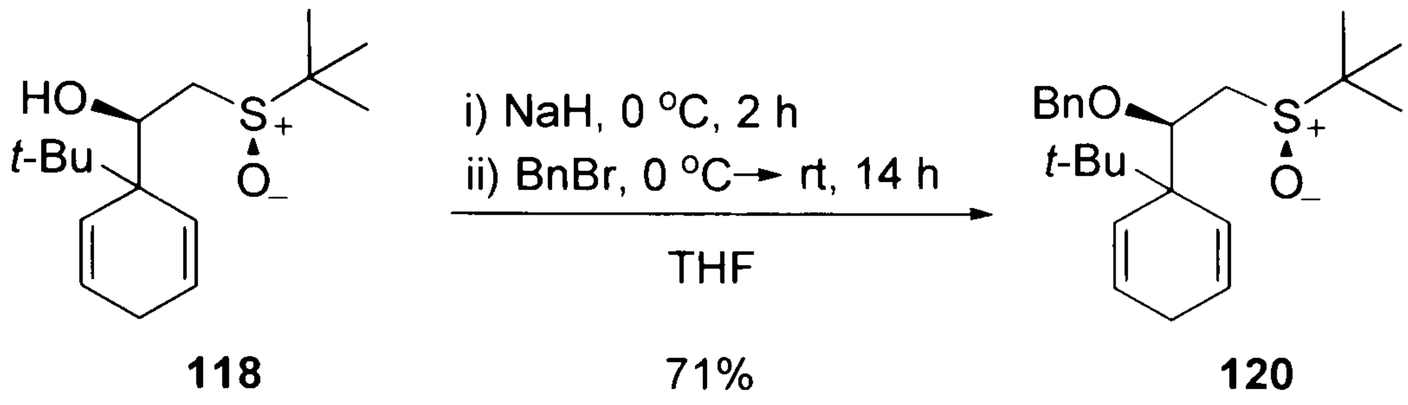
Attempts to effect the cyclisation of silyl ether **119** failed due to decomposition of the starting material under the thermolysis conditions as shown in Scheme 77.



119 **119a** **119b**

Scheme 77

Alcohol **118** was next protected as a benzyl ether (Scheme 78).

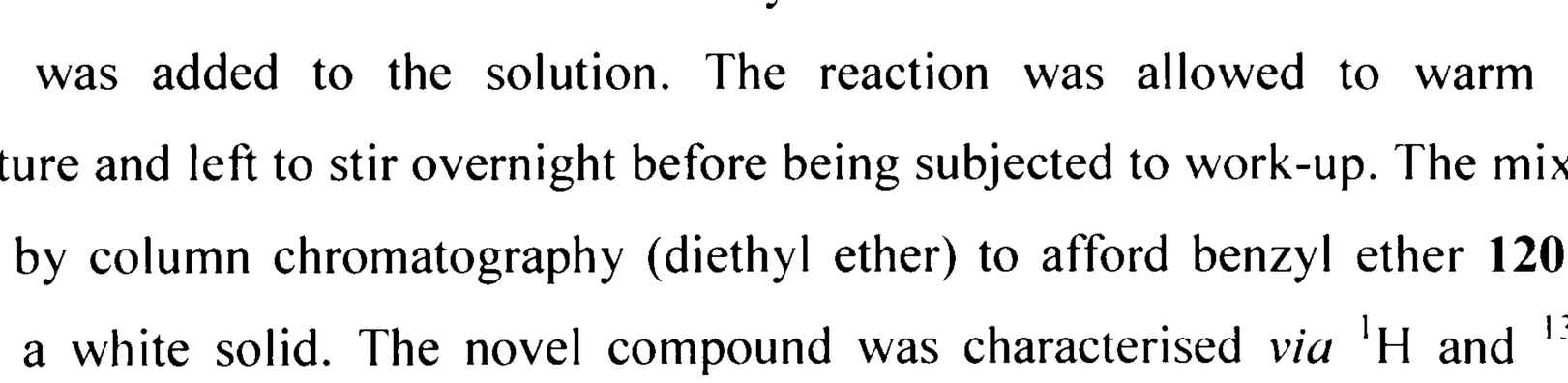


118 71% **120**

Scheme 78

Sulfoxide **118** was stirred with sodium hydride for two hours at 0 °C before benzyl bromide was added to the solution. The reaction was allowed to warm to room temperature and left to stir overnight before being subjected to work-up. The mixture was purified by column chromatography (diethyl ether) to afford benzyl ether **120** in good yield as a white solid. The novel compound was characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry, IR spectroscopy and melting point analysis.

The protected alcohol **120** was next submitted to the thermolysis conditions (Scheme 79).



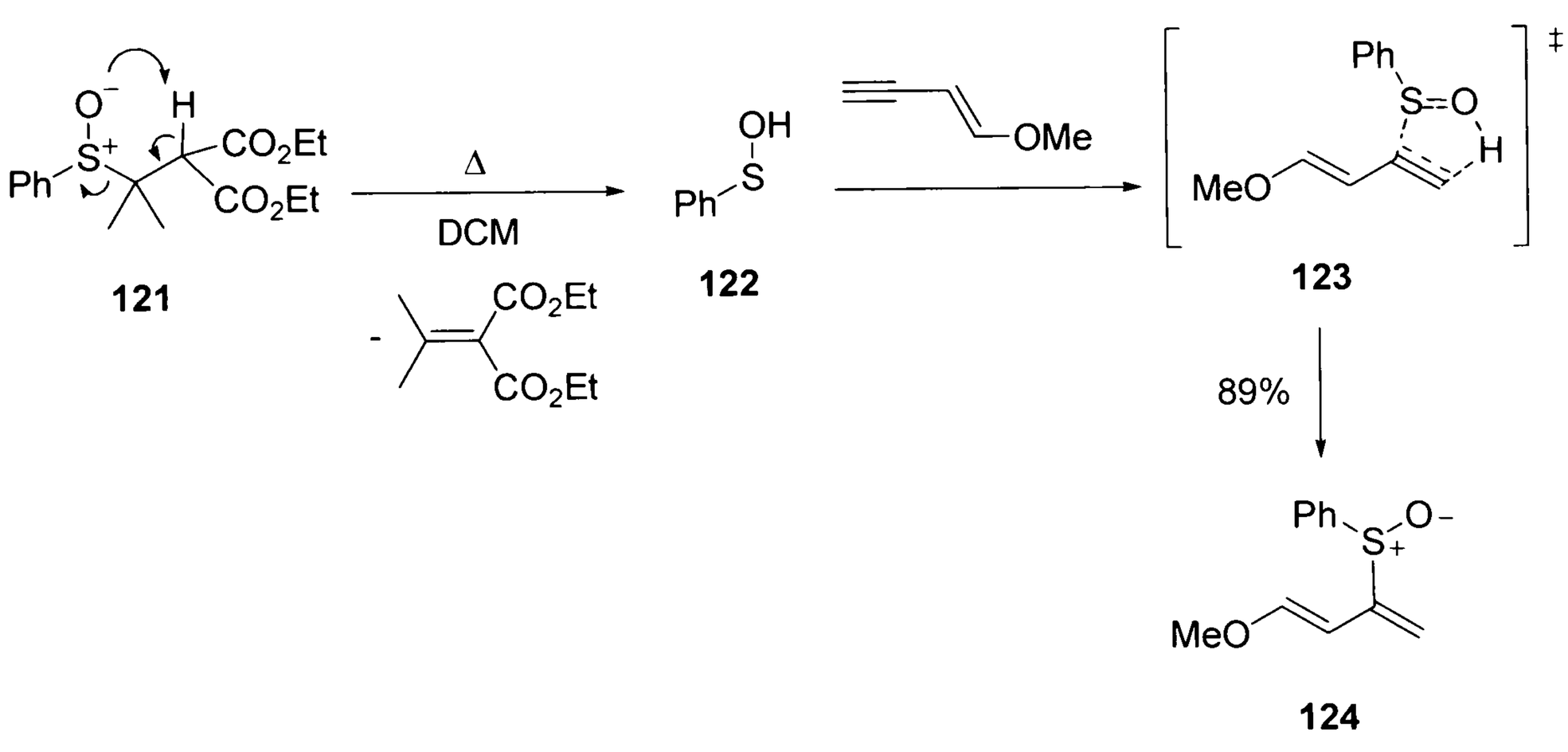
120 8% **120a** **120b**

Scheme 79

After one hour of reflux in xylene, the reaction appeared to be decomposing by thin layer chromatography. It was therefore immediately submitted to purification by column chromatography (diethyl ether). This resulted in the recovery of 62% of unreacted starting material and just 8% of a novel cyclic sulfoxide **120a** or **120b**, which was characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry and IR spectroscopy. The configuration of the novel compound could not be determined.

The cyclisation precursors with *t*-butyl at the *ipso* position, all showed a certain degree of incompatibility with the reaction conditions (refluxing xylene) and afforded the cyclic sulfoxides in moderate to poor yields.

In the literature, there is precedent for a number of sulfoxide eliminations, which are induced at a lower temperature than refluxing xylene (Scheme 80).[65]



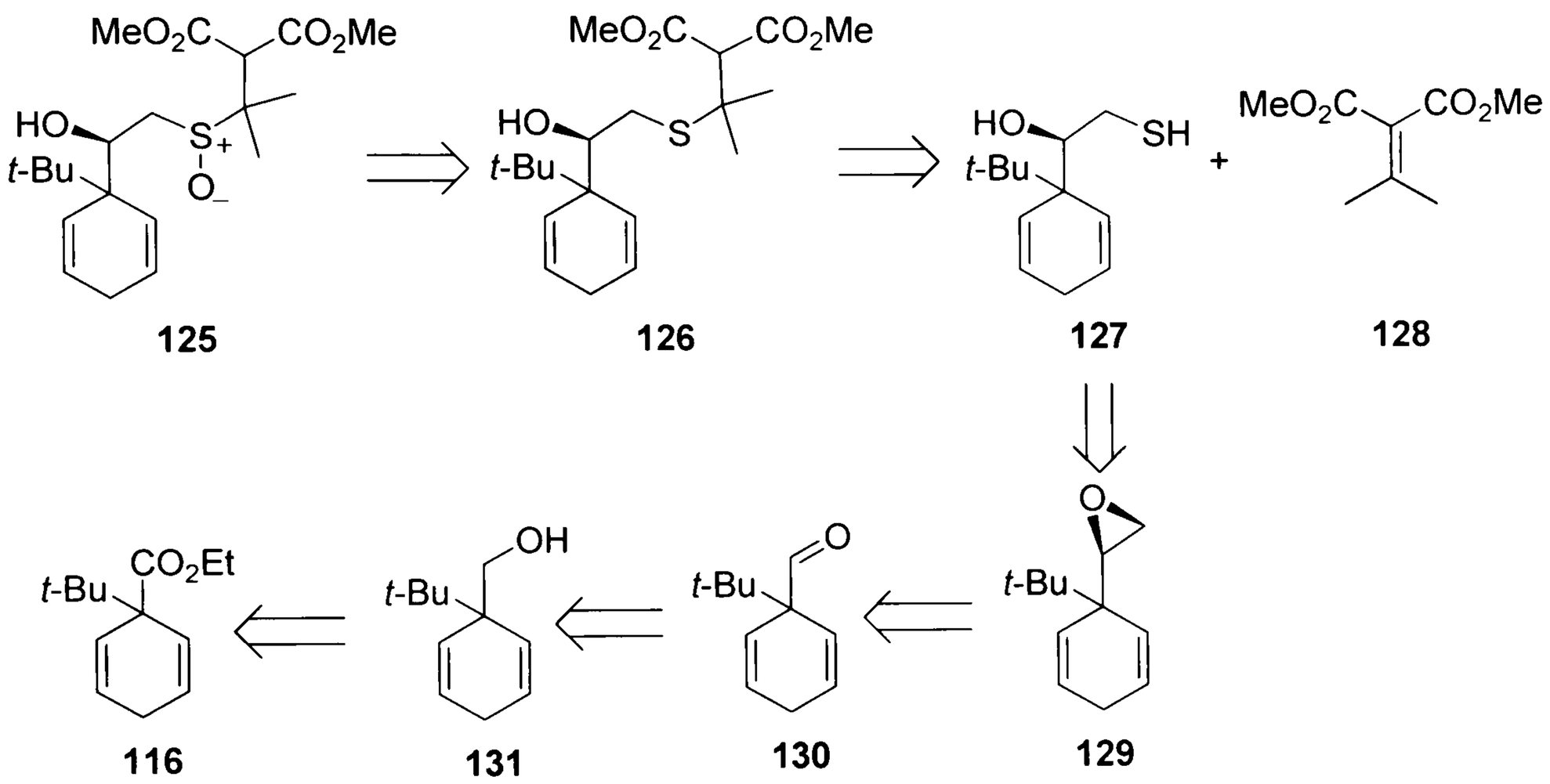
Scheme 80

The presence of two electron-withdrawing groups in a ß-position to the sulfoxide in **121** increases the facility with which the sulfoxide can abstract the acidic α-hydrogen of the malonate ester, to give rise to the intermediate sulfenic acid **122**. The sulfenic acid

formed was then used by Jones *et al* to perform a chemo- and regioselective addition to the ene-yne substrate to afford the diene **124**.

Structural variations of substrate **118** to **125** could permit the cyclisation to occur under milder reaction conditions and presumably this in turn should prevent unwanted side reactions (Scheme 81). This would also facilitate a greater insight into the origin of the selectivity of the cyclisation process (see Section 2.4).

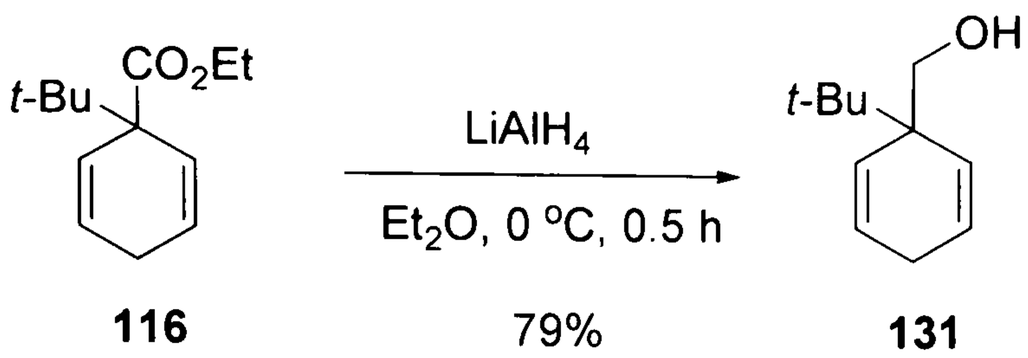
A retrosynthetic outline for compound **125** is shown in Scheme 81.



Scheme 81

Sulfoxide **125** could derive from oxidation of sulfide **126**, which in turn could come from conjugate addition of thiol **127** to the electrophile α,β-unsaturated di-ester **128**, which is commercially available. The ß-hydroxy thiol **127** could be made by regioselective opening of epoxide **129**, which is derived from aldehyde **130**. The aldehyde **130** could in turn come from alcohol **131**. The alcohol **131** comes from the reduced ester, the Birch reduction product of ethyl benzoate.

Synthesis of alcohol **131** is outlined in Scheme 82.

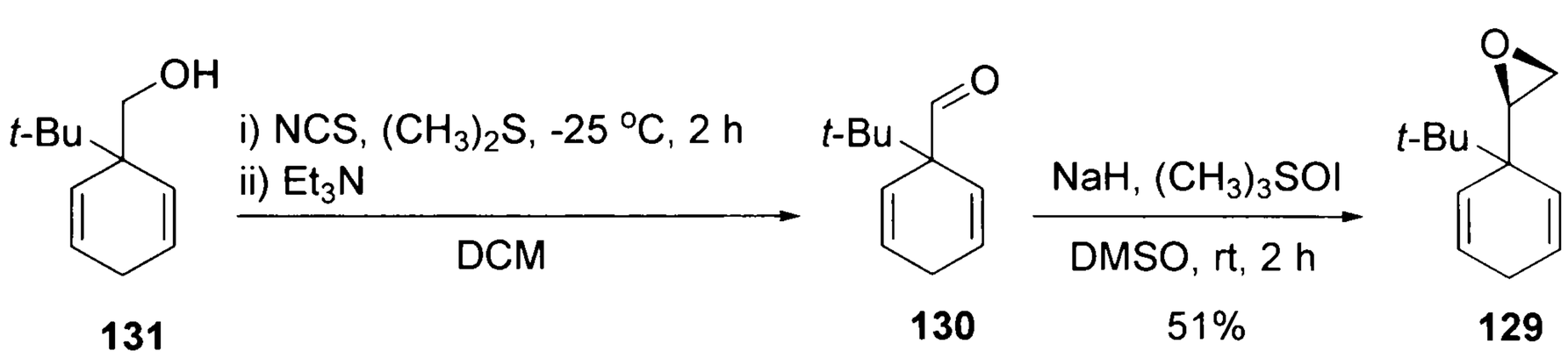


116 79% **131**

Scheme 82

Reduction of ethyl ester **116** with lithium aluminum hydride afforded the novel alcohol **131** as a white solid, which was deemed pure enough by ^{1}H NMR spectrum to not require further purification. The compound **131** was characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry, IR spectroscopy and melting point analysis.

The alcohol **131** was next converted to aldehyde **130**,[51] followed by further synthetic manipulation to epoxide **129** (Scheme 83).[66]

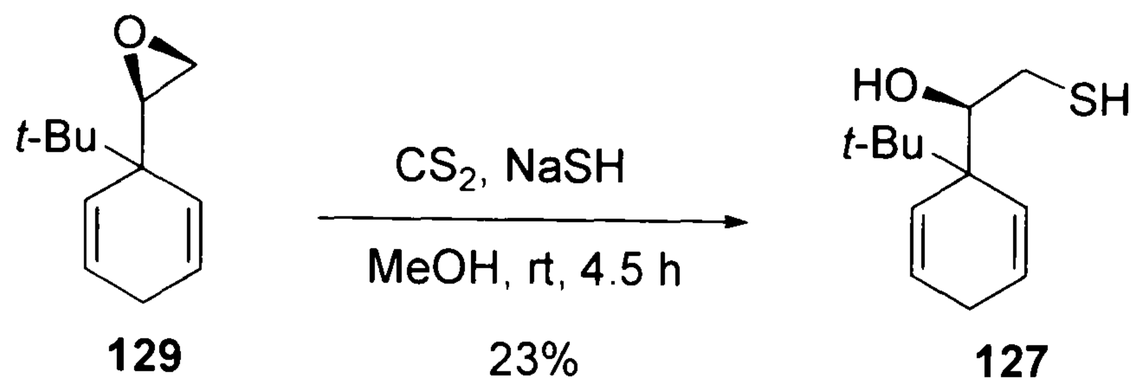


131 **130** 51% **129**

Scheme 83

Oxidation of alcohol **131** afforded the aldehyde **130**, which was carried through to the next step without any further purification. The aldehyde **130** was reacted with trimethylsulfoxonium iodide to give the epoxide **129**, which was purified by column chromatography (diethyl ether), basified with triethylamine. The novel compound **129** was fully characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry and IR spectroscopy.

The epoxide **129** was then regioselectively opened with sodium hydrosulfide (Scheme 84).[67]

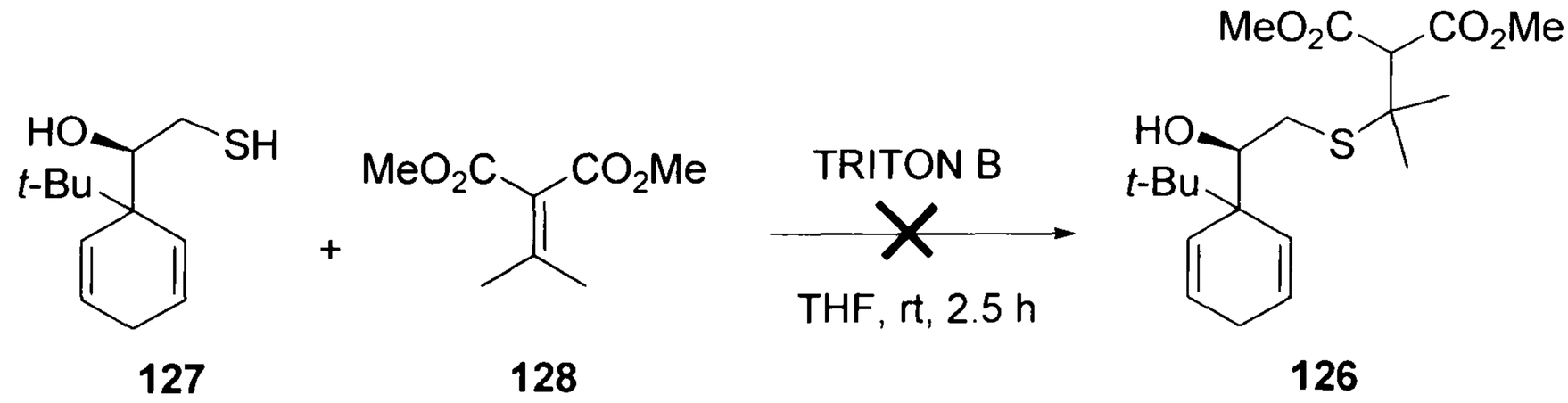


129 **127**

Scheme 84

The epoxide **129** was stirred for 4.5 hours with the reagents before the crude thiol **127** was isolated. Purification by column chromatography (5:95 diethyl ether/60-80 °C petroleum ether) afforded the novel compound **127** in low yield. The thiol **127** was characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry and IR spectroscopy.

Attempts to effect the Michael addition of nucleophile **127** with the α,β-unsaturated di-ester **128** proved futile (Scheme 85).



127 **128** **126**

Scheme 85

The procedure reported by Jones *et al*[65] for their synthesis of sulfoxide **121** (see Scheme 80) was followed for the Michael addition of thiol **127** onto substrate **128**. It may be that the alcohol functionality in **127** competes with the thiol in reacting with substrate **128**. However, no characterisable products were isolated.

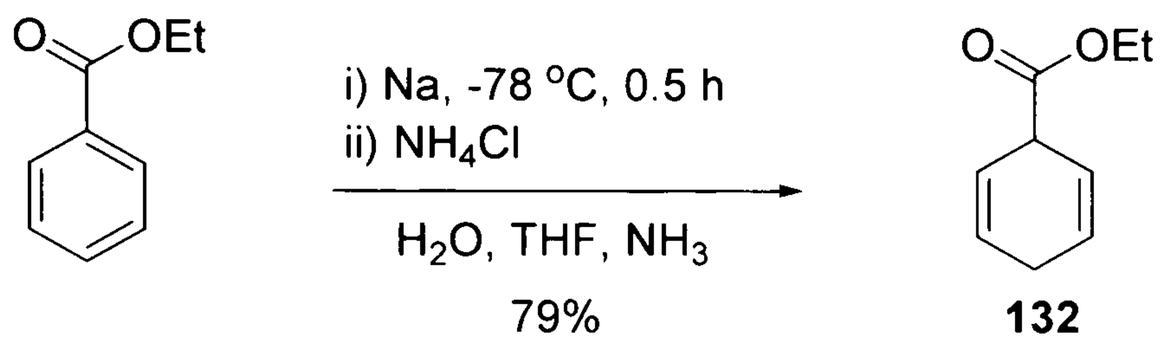
At this stage of the project the attempted synthesis of **125** was abandoned.

In summary, it has been demonstrated that different alkyl substituents at the *ipso* position of the cyclisation precursor induce different selectivity in the cyclisation for the formation of the corresponding cyclic sulfoxides. However, modest yields, difficulty in determining the relative configurations of the products isolated and the irreproducibility of some of the earlier results discouraged any further experimental investigation, towards a definitive conclusion of the selectivity observed for the cyclisation.

Section 2.6: Synthetic manipulations *en route* to breynolide

In breynolide, the perhydrobenzothiophene system is characterised by *cis* fused hydrogens at the bridgehead. Therefore, the synthesis of a cyclisation precursor with hydrogen at the *ipso* position of the diene ring was an obvious synthetic target for investigation. Although an initial approach towards this goal had failed (Section 2.2), it was deemed appropriate to try the direct coupling of **75** with ethyl ester **132**.

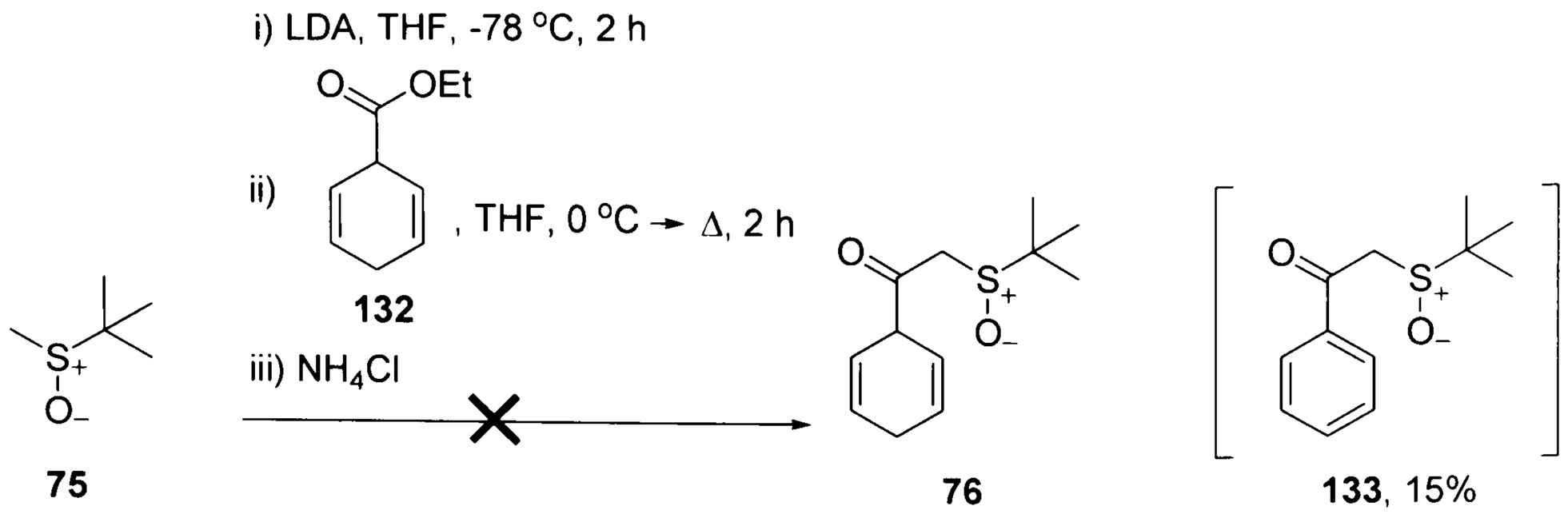
With this in mind, ethyl benzoate was reduced to the 1,3-diene **132** as depicted in Scheme 86.



Scheme 86

Following a reported procedure,[68] Birch reduction of ethyl benzoate and a quench of the resultant anion with ammonium chloride afforded the diene **132** (lit.[68] 64%). The product was carried through to the next step of the synthesis without further purification following a standard work-up procedure.

The attempted condensation of ethyl ester **132** with the anion of *t*-butyl methyl sulfoxide **75** to afford ß-keto sulfoxide **76**, however, failed (Scheme 87).



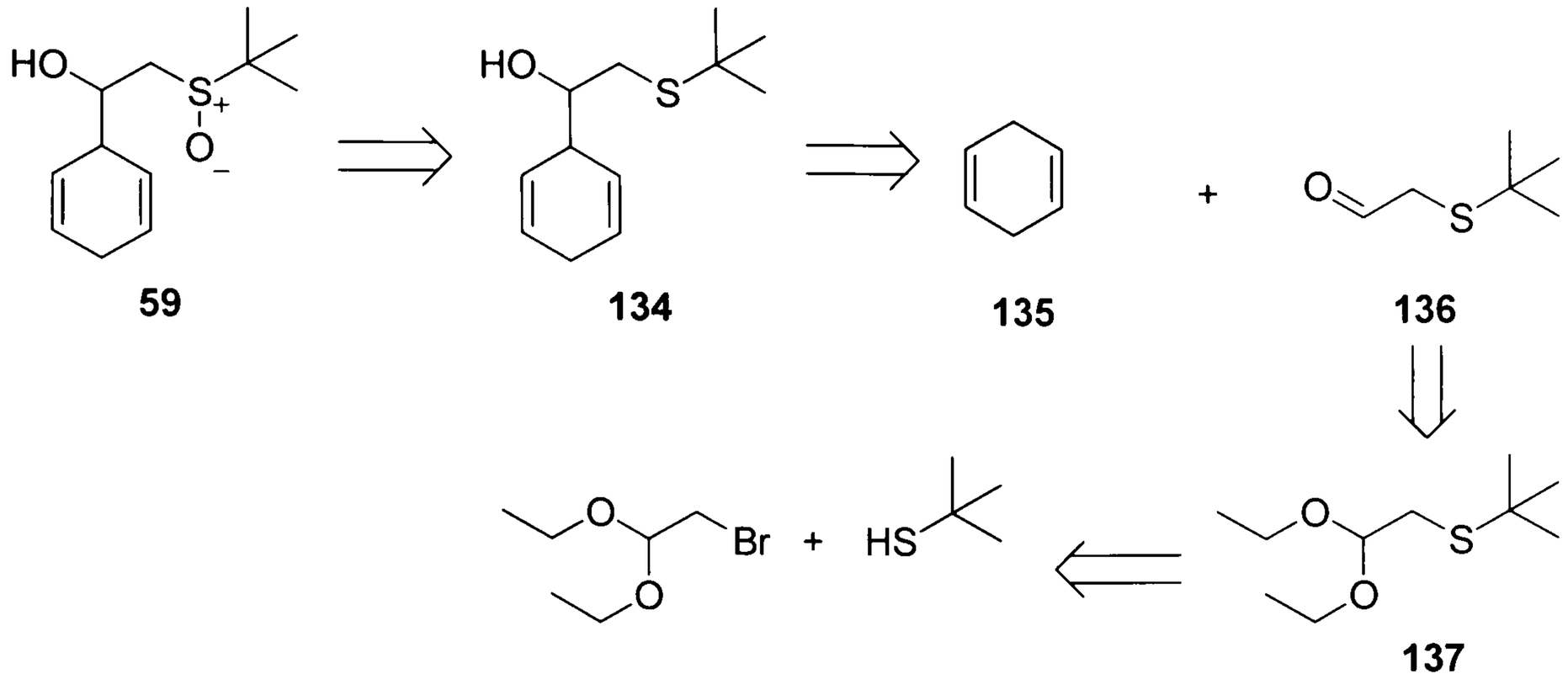
75 **76** **133**, 15%

Scheme 87

It may be that the *t*-butyl methyl sulfoxide anion acted as a base rather than a nucleophile, abstracting the acidic hydrogen at the *ipso* position. The aromatic ketone **133** could be isolated from the reaction in 15% yield. None of the desired ß-keto sulfoxide **76** was observed.

The synthetic approach used in the case of alkyl substituents at the *ipso* position could not therefore be applied to the synthesis of substrate **59** carrying a hydrogen at the *ipso* position.

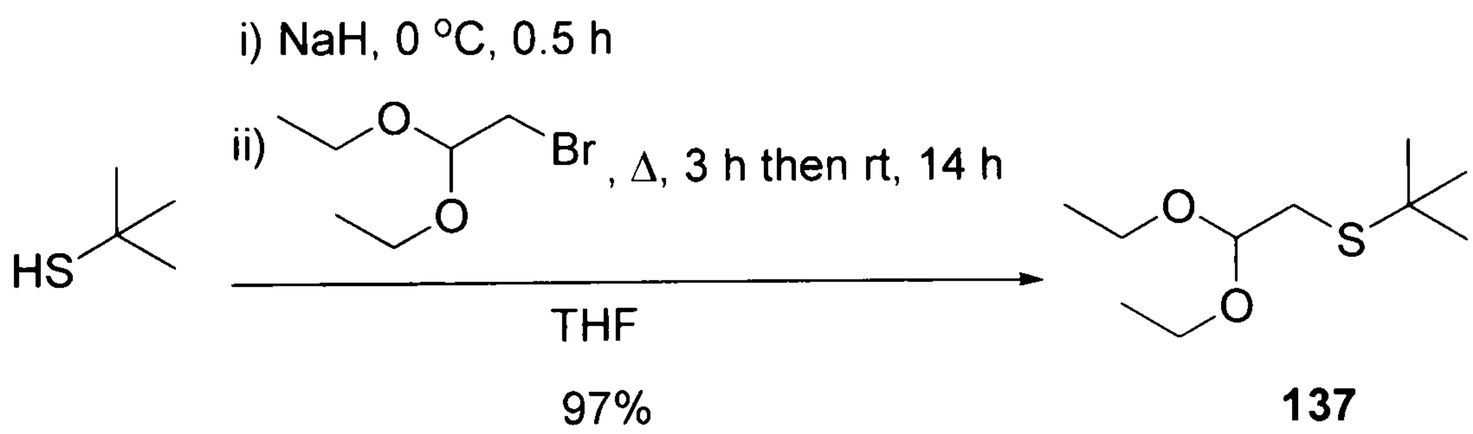
It was therefore thought to approach the synthesis of **59** *via* the formation of the carbon-carbon bond between the diene system and the alkyl chain. The alternative retrosynthetic analysis to **59** that was proposed is outlined in Scheme 88.



Scheme 88

Sulfoxide **59** could come from oxidation of sulfide **134**. Alcohol **134** could be the product of condensation between the anion of cyclohexadiene **135** and the aldehyde **136**. The aldehyde **136** is the hydrolysis product of acetal **137**, which in turn comes from condensation of two commercially available reagents, *t*-butyl thiol and 2-bromoacetaldehyde diethyl acetal.

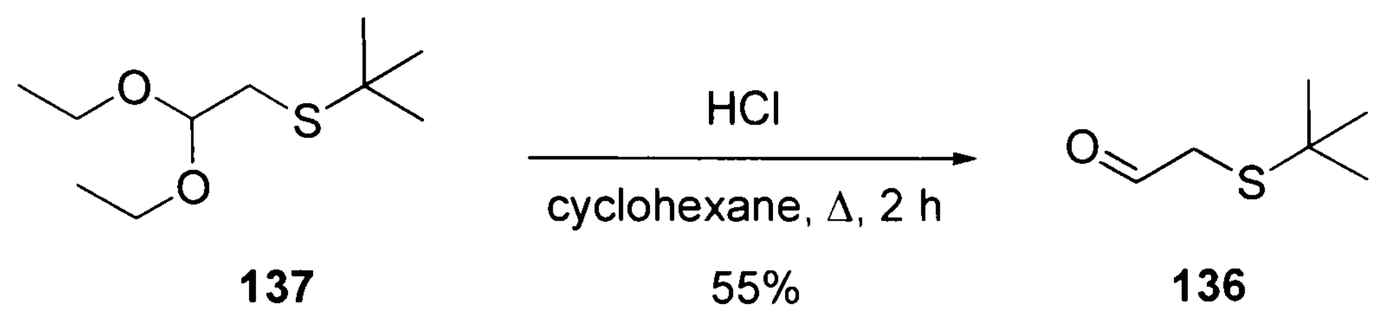
A literature procedure was followed for the synthesis of sulfide **137** (Scheme 89).[69]



Scheme 89

t-Butyl thiol was stirred for half an hour before 2-bromoacetaldehyde diethyl acetal was added to the solution. The reaction was left to go to completion overnight, as monitored by thin layer chromatography, and was then subjected to standard work-up procedures to afford product **137**. The isolated product was deemed pure enough to carry through to the next step by analysis of its corresponding ^{1}H NMR spectra.

Hydrolysis of acetal **137** afforded aldehyde **136** (Scheme 90).[69]

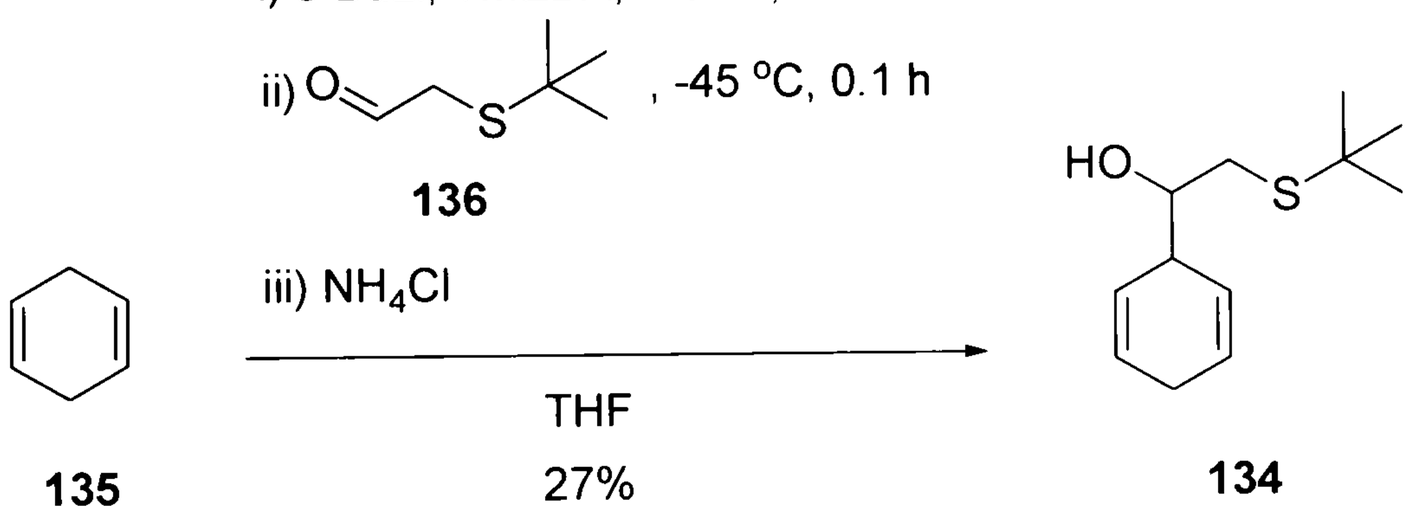


137 **136**

Scheme 90

Aldehyde **136** was isolated in modest yield from the corresponding hydrolysis of acetal **137**. The low yield might be a reflection of the volatility of **136**. Again the isolated product was deemed pure enough to carry through to the next step.

Condensation of aldehyde **136** with the anion of diene **135** proved problematic (Scheme 91).[70]



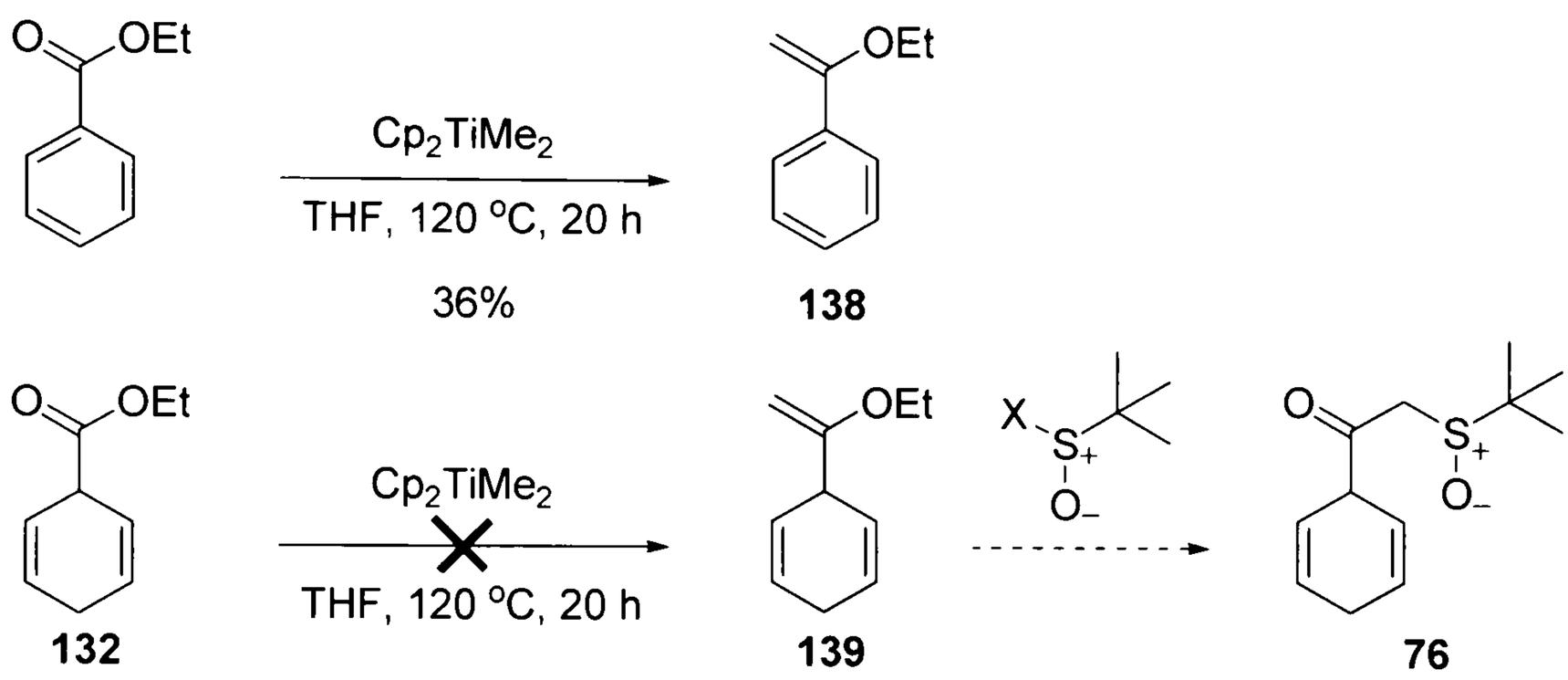
Scheme 91

Diene **135** was deprotonated using a known literature procedure.[70] The reaction flask which contained the diene **135**, *s*-butyllithium and *N,N,N',N'*-tetramethylethylenediamine, was brought from -78 °C to -45 °C to ensure the formation of the corresponding anion of **135**. To the yellow solution was next added a solution of aldehyde **136** in THF. After 5 minutes, the reaction was worked-up. Purification by column chromatography (4:6 diethyl ether/ 60-80 °C petroleum ether) afforded one main isolable product in poor yield, which could be identified as **134**. However, this was not

pure enough to carry through to the synthesis of **59** and further modification of the reaction conditions did not prove successful.

A different approach to the synthesis of ß-keto sulfoxide **76** was then investigated.

Literature precedent for the transformation of esters to the corresponding enol ethers encouraged studies towards the formation of enol **139**, employing similar methodology (Scheme 92).[71] Substrate **139** could potentially be reacted with an electrophilic source of sulfur to give the corresponding ß-keto sulfoxide **76**.

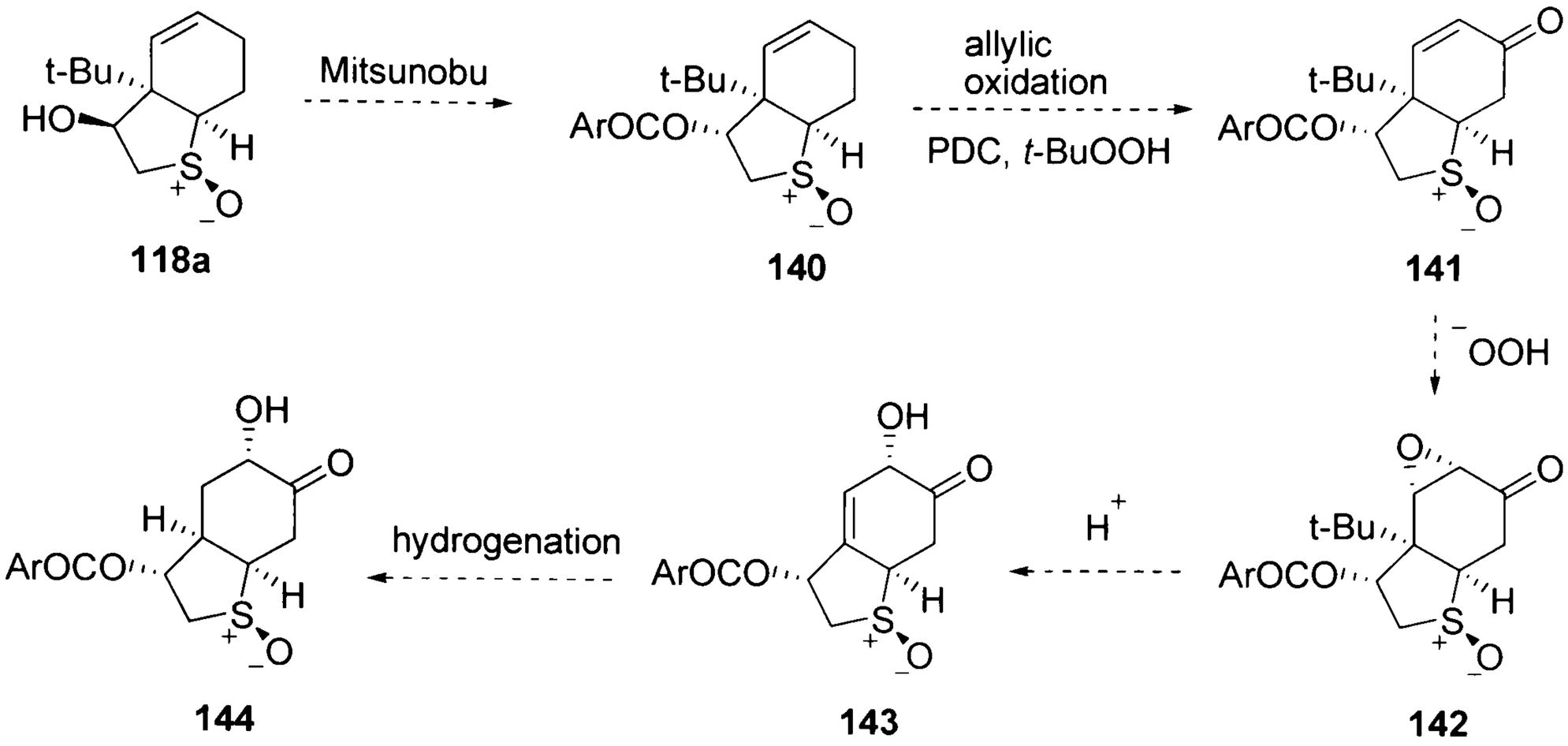


Scheme 92

The literature procedure was first tested on ethyl benzoate.[71] The freshly prepared Tebbe-Petasis reagent gave the desired product **138** in 36% yield. The yield was based on ^{1}H NMR analysis of the crude compound. However, attempts to affect the conversion of ester **132** to the enol ether **139** resulted in the complete recovery of starting material.

It was felt that if it was not possible to have a hydrogen at the *ipso* position in the cyclisation precursor, an alternative strategy would be to have a different substituent at the *ipso* position that could then be manipulated, after cyclisation, to give the perhydrobenzothiophene fragment of breynolide possessing a hydrogen at the bridgehead.

Substrate **118a** seemed ideal and possible removal of the *t*-butyl group at the bridgehead as a carbocation encouraged further manipulations of the previously synthesised compound. The idea is outlined in Scheme 93.

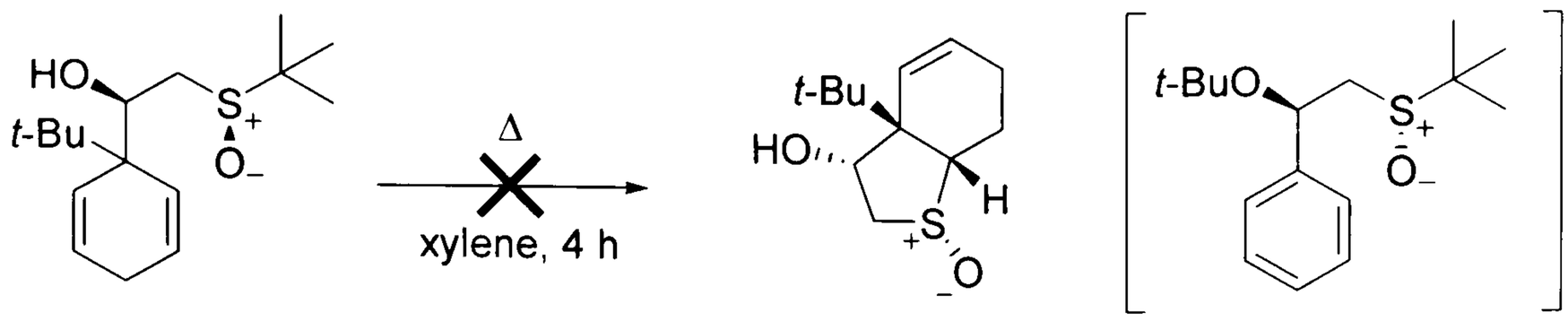


118a **140** **141** **142** **143** **144**

Scheme 93

The cyclic sulfoxide **118a** has to be converted into its diastereoisomer with the right configuration for the synthesis of breynolide. It could be converted to protected alcohol **140** *via* a Mitsunobu reaction. Allylic oxidation would give ketone **141**, which could be epoxidised to afford **142**. Mild acidic conditions could favour the opening of the epoxide with the concomitant *t*-butyl group removal. The hydrogenation driven by substrate control could give the desired intermediate for the synthesis of breynolide.

Unfortunately, attempts to reproduce the earlier cyclisation results for compound **118** failed due to decomposition of the starting material **118** under the reaction conditions and the formation of compound **145** in poor yield (Scheme 94).



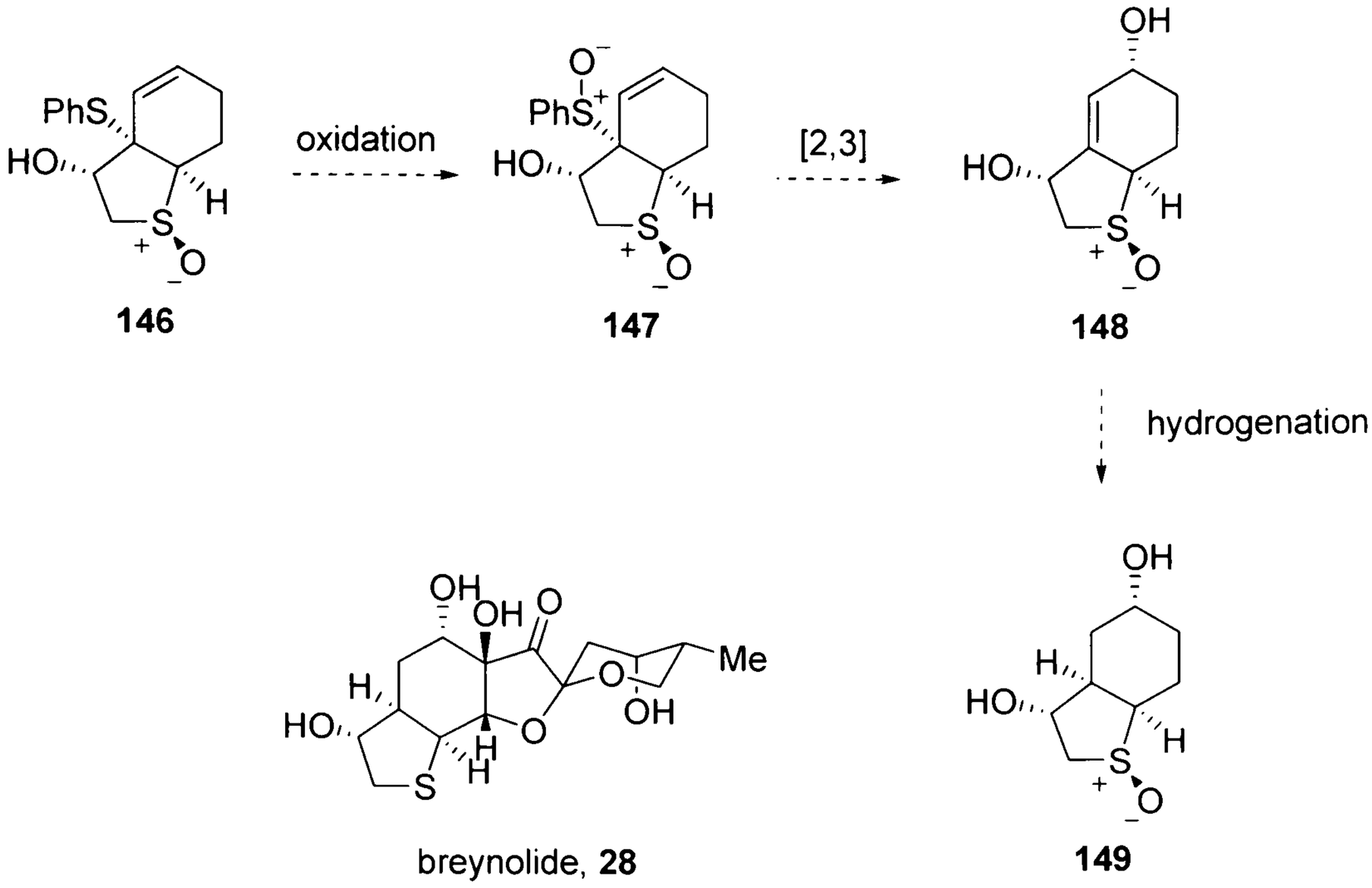
118 **118a** **145**, 9%

Scheme 94

To overcome the capricious nature of the reaction, it was thought to wash the glassware with a basic or acidic solution, to avoid possible side reactions. A basic or acidic wash of the glassware did not alleviate the problem. Use of a radical suppressor, such as 2,6-di-*t*-butyl-4-methylphenol, also resulted in decomposition of starting material. Lowering the temperature of the reaction at which reflux was conducted, in *n*-octane, did not improve the outcome.

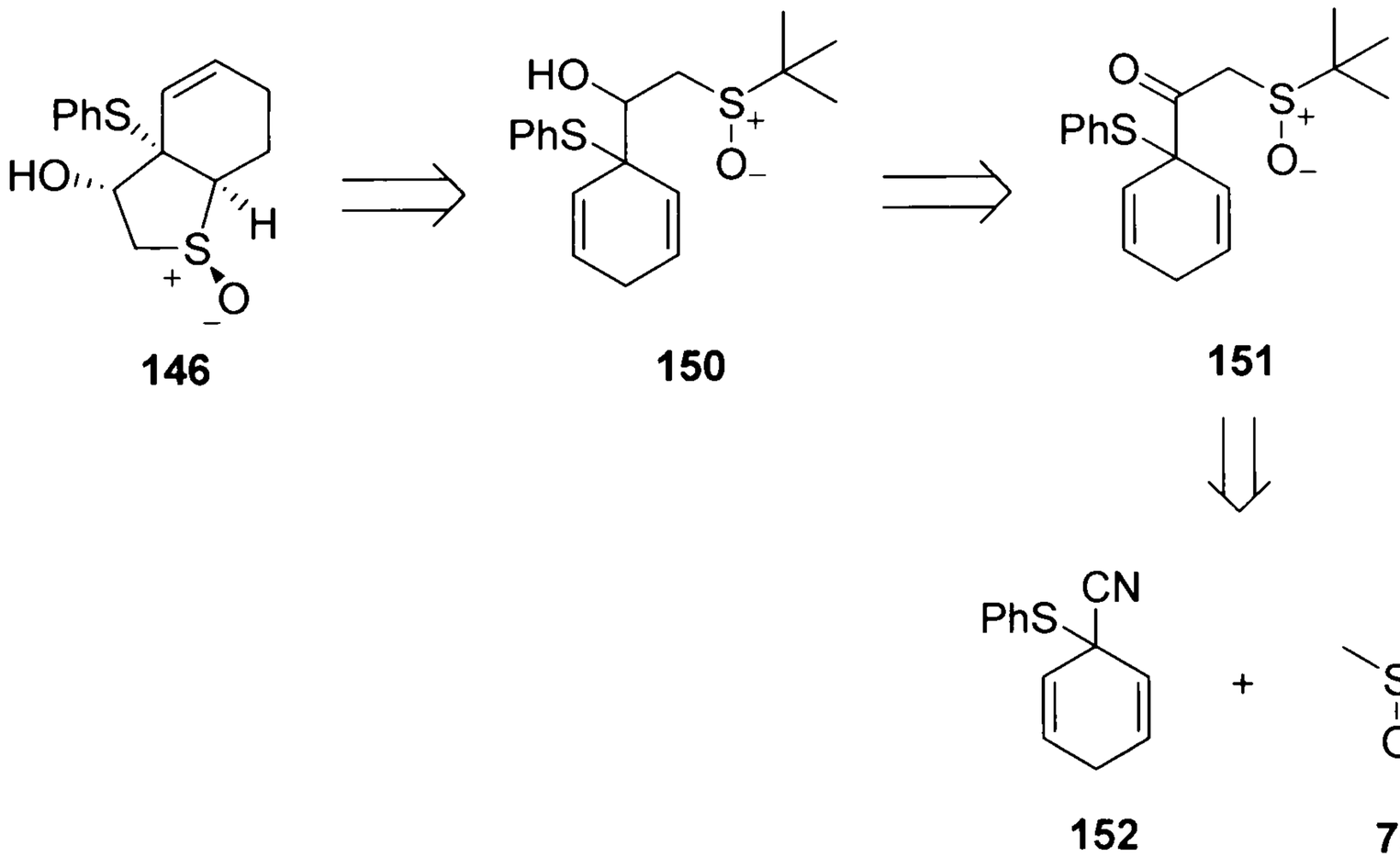
An alternative approach to the synthesis of the perhydrobenzothiophene fragment of breynolide possessing a hydrogen at the bridgehead was then adopted.

The strategy is outlined in Scheme 95. The cyclic sulfoxide **146** has a thioether at the bridgehead and *via* a series of synthetic manipulations: oxidation and a 2,3-sigmatropic rearrangement followed by hydrogenation (possibly driven by substrate control), would give cyclic sulfoxide **149**, with four stereocentres set with the correct configuration for the synthesis of breynolide.



Scheme 95

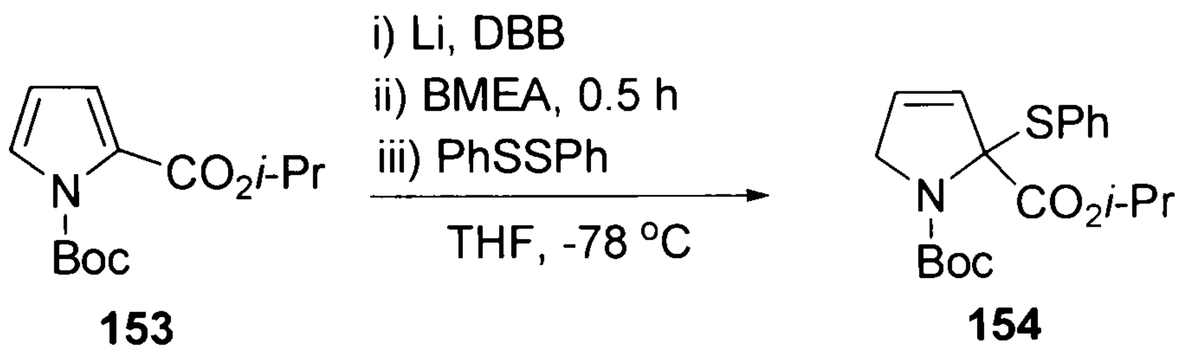
Cyclic sulfoxide **146** can derive from a cyclisation precursor with the thiophenyl substituent at the *ipso* position. A retrosynthetic outline for this compound is shown below (Scheme 96).



Scheme 96

Perhydrobenzothiophene-S-oxide **146** can derive from the cyclisation precursor **150**, which is the product of the reduction of ketone **151**. ß-Keto sulfoxide **151** is the result of condensation between the anion of *t*-butyl methyl sulfoxide **75** and the nitrile **152**. The 1,3-diene **152** could come from commercially available benzonitrile.

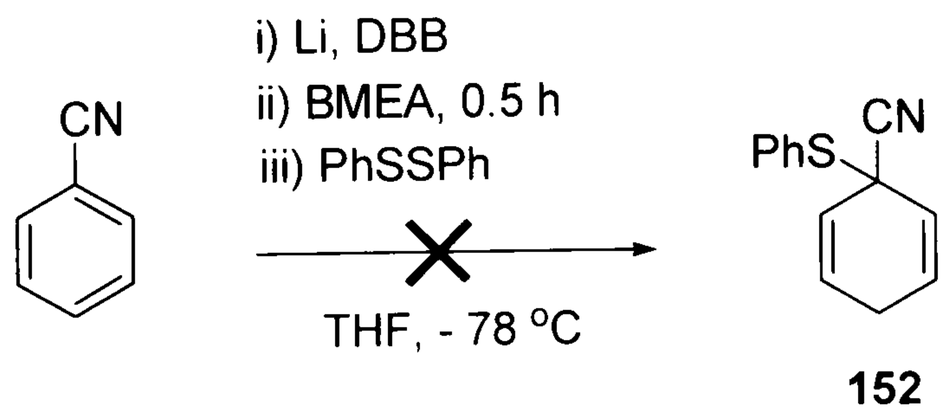
For the synthesis of compound **152**, a recent publication seemed promising.[72] Donohoe *et al* have recently reported the use of phenyl disulfide as an electrophile to quench the anion produced by reduction of a substituted pyrrole **153** (Scheme 97).



Scheme 97

The reaction conditions were also tested on benzonitrile, but with alternative electrophiles.

The idea was to test these conditions on benzonitrile for the synthesis of 1,3-diene **152** (Scheme 98).



Scheme 98

Benzonitrile and bis(methoxyethyl)amine was added to a solution of lithium 4,4`-di-*t*-butylbiphenyl in THF at -78 °C and stirred for 0.5 hours. Phenyl disulfide was next added and the colour of the solution was observed to turn from turquoise to yellow. After work-

up, the crude reaction was purified by column chromatography (60-80 °C petroleum ether), without isolating any of the desired product **152**. Modifications of the reaction conditions proved futile.

At this late stage of the project the idea of inserting a hetero-substituent at the *ipso* position was abandoned.

Section 2.7: Summary

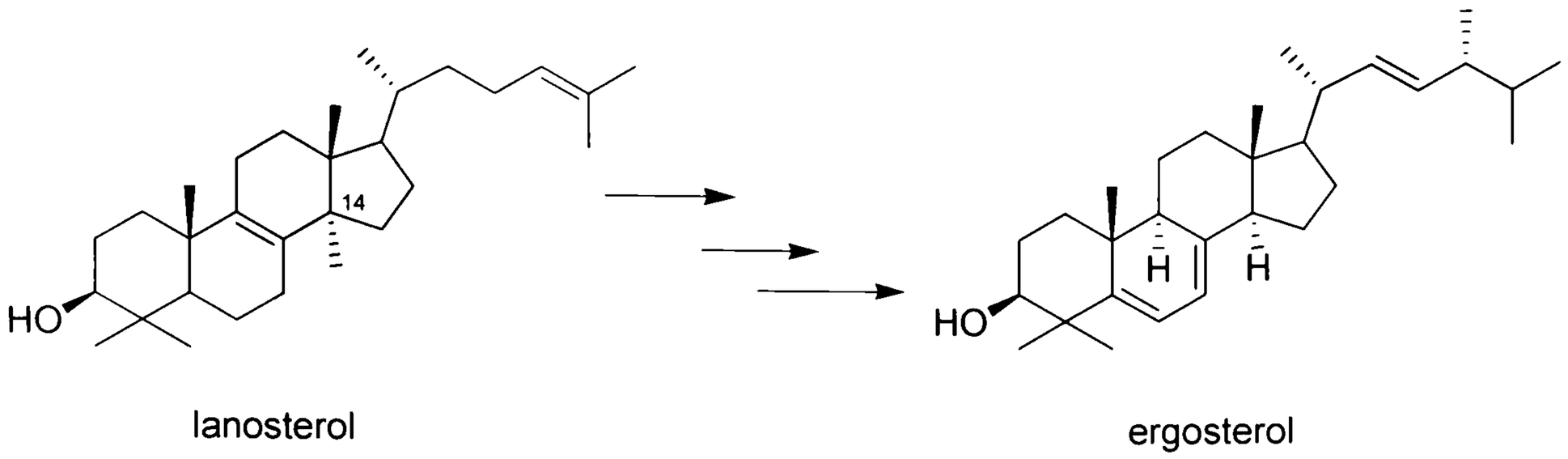
A concise study has been reported on the formation of the perhydrobenzothiophene-S-oxide system *via* a tandem sulfoxide elimination – sulfenic acid addition, where the precursor is characterised by a diene ring and *t*-butyl sulfoxide tethered *via* an alkyl side chain. It has been demonstrated that a substituent on the alkyl chain (specifically a protected alcohol) can act as a stereochemical control element, inducing reasonable levels of stereoselectivity (see Section 2.3, Table 2). Studies on the origin of the selectivity have suggested the reaction is under thermodynamic control, as a result of reversibility of sulfoxide elimination-sulfenic acid addition reaction (see Section 2.4). The effect of different substituents at the *ipso* position of the diene ring has also been investigated, and led in one case to the exclusive formation of one cyclic diastereoisomer, with the *t*-butyl group at the *ipso* position and the unprotected alcohol on the alkyl chain (see Section 2.5). The irreproducibility of the result prevented further studies over the origin of the selectivity for the cyclisation. Finally, an attempt to apply this methodology towards the synthesis of breynolide, which contains the perhydrobenzothiophene fragment, has to-date not proven successful (see Section 2.6).

Chapter 3

Section 3.1: Introduction and background to antifungal agents

Most fungal infections (mycoses) involve superficial invasion of the skin or the mucous membranes of body orifices. These diseases, which can usually be controlled by local application of an antifungal agent, are conveniently divided into two classes: (1) contagious superficial epidermal infections caused by various species, and (2) mycoses caused by pathogenic yeasts which are contagious and usually superficial infections involving the skin and mucous membranes. Some species of yeasts (*Aspergillus*, *Candida*, *Cryptococcus*) under certain conditions are capable of invading deeper body cavities and causing systemic mycoses.[73] Such infections might become serious and occasionally life-threatening, and they are quite difficult to treat. The treatment of systemic mycoses has acquired increased importance in recent years as a result of the increased incidence of yeast infections in patients. Fatty acids, copper and zinc salts, aromatic acids and alkylated or halogenated phenols are all useful for the treatment of local fungal infections. Research at the Janssen Laboratories in Belgium during the 1960s led to the discovery that certain highly substituted and lipophilic imidazoles possessed useful broad-spectrum antifungal activity. Since this discovery, numerous similar imidazoles and analogous 1,2,4-triazoles have been introduced throughout the world for the treatment of fungal infections.[74] Despite the progress that has been made in antifungal drug discovery, relatively few agents have been found that combine the properties required for the treatment of systematic yeast infections, namely, effectiveness against the causative organisms and a reasonable margin of safety. The search for better antifungal agents with increased specificity towards fungal enzymes remains a primary target in medicinal chemistry research.

The azoles represent a class of versatile antifungal agents, where azoles designate agents bearing either an imidazole or 1,2,4-triazole ring. At low concentrations, azole antifungal antibiotics cure mycoses by selectively inhibiting the fungal membrane-bound enzyme $P450_{14DM}$ (lanosterol 14α-demethylase enzyme).[75] This enzyme is essential for the biosynthesis of ergosterol, the principal component of fungal cell membranes (Scheme 99).



lanosterol

ergosterol

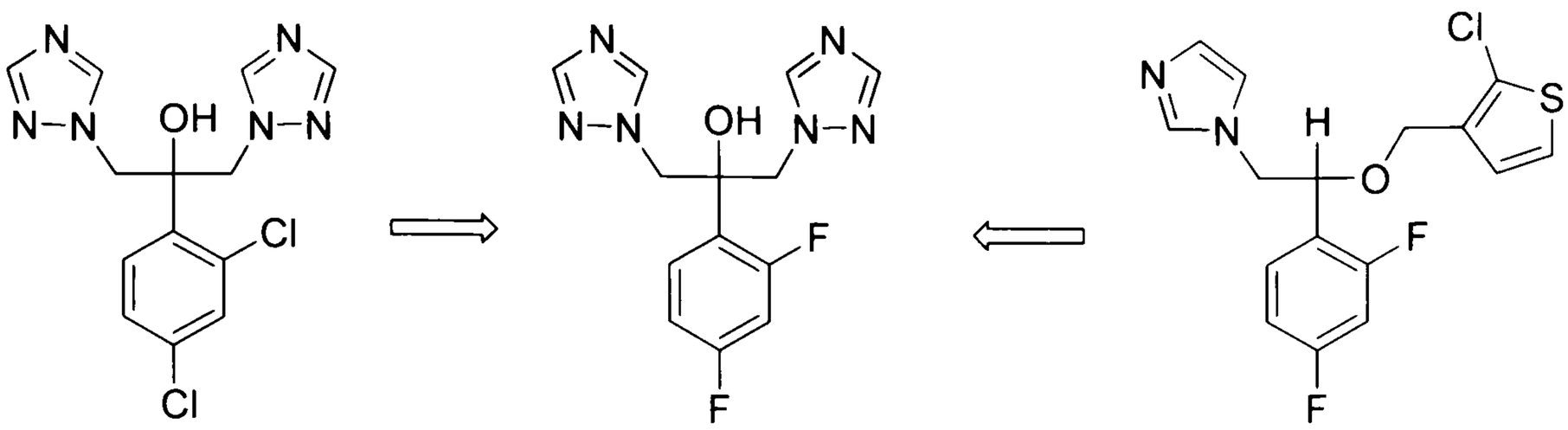
Scheme 99

The accumulation of 14α-methylated sterols in azole-treated fungal cells affects membrane structure and functions, resulting in an inhibition of the growth of fungi.

The primary structural requirement for members of the azole class is a weakly basic imidazole or 1,2,4-triazole ring (pK_a in the range of 6.5-6.8) bonded by a nitrogen-carbon linkage to the remaining structure. The amidine nitrogen atom (N-3 in the imidazoles; N-4 in the triazoles) is believed to bind the heme iron of enzyme-bound cyt P450 to inhibit activation of molecular oxygen and prevent oxidation of steroidal substrates by the enzyme. The more potent antifungal azoles possess two or three aromatic rings, at least one of which is halogen-substituted and other non-polar functionality. Presumably, the extensive non-polar portion of these molecules mimics the correspondingly non-polar steroidal portion of the substrate for lanosterol 14α-demethylase, in shape and size. The non-polar functionality confers a high degree of lipophilicity to the antifungal azoles. The free bases are generally insoluble in water, but soluble in most organic solvents.

Fluconazole is a water-soluble bis-triazole with broad-spectrum antifungal properties. Apparently the presence of two weakly basic triazole rings in the molecule confers sufficient aqueous solubility to balance the lipophilicity of the 2,4-difluorophenyl group. It is sufficiently water soluble to be injected intravenously as a solution of the free base.

The Pfizer drug design team discovered the clinically successful drug fluconazole after manipulations of less active analogues (Scheme 100).[76]



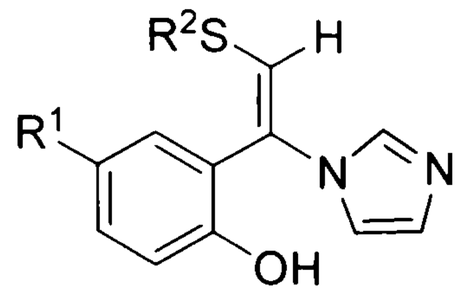
UK-47265 Fluconazole Tioconazole

Scheme 100

The antifungal agent UK-47265 was an extremely promising antifungal agent, but *in vivo* tests on mice, dogs, and rats showed that it affected liver toxicity and was potentially teratogenic. The design team manipulated the compound to a difluoro-substituted one and found the potent drug fluconazole. Moreover, the antifungal agent tioconazole is only used for skin infections because of its non-polar nature and poor solubility in blood. The introduction of a polar hydroxyl group and more polar heterocyclic rings led to the orally active antifungal agent fluconazole with improved solubility and enhanced activity against systemic infection.

In recent years, studies have concentrated on the development of more powerful antifungal agents and several groups from every corner of the globe have contributed to this challenge. A brief summary of this research is outlined below.

In the quest to find more potent and broad-spectrum antifungal agents, Matsuda and coworkers synthesised ß-sulfur substituted vinylimidazole derivatives **155** which show enhanced activity over other antifungal agents against a variety of fungi including yeast cells (Figure 9).[77]

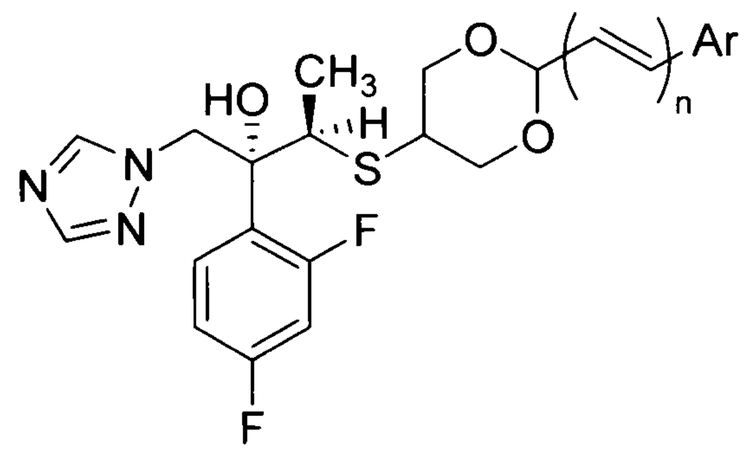


155

Figure 9

The antifungal activity of 1,2,4-triazole derivatives of 2,2,5-substituted tetrahydrofuran compounds has also been screened with promising initial results obtained.[78]

Oida *et al* designed a new series of dioxane-triazole compounds **156** (Figure 10).[79]

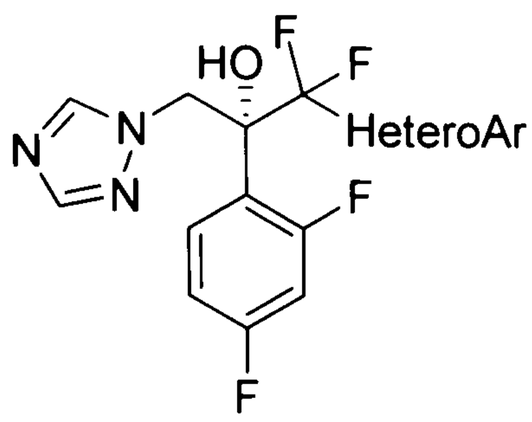


156

Figure 10

The derivatives bearing an aromating ring substituted with an electron-withdrawing group in the side chain showed excellent *in vivo* activities against *Candida*, *Aspergillus* and *Cyptococcus* species.

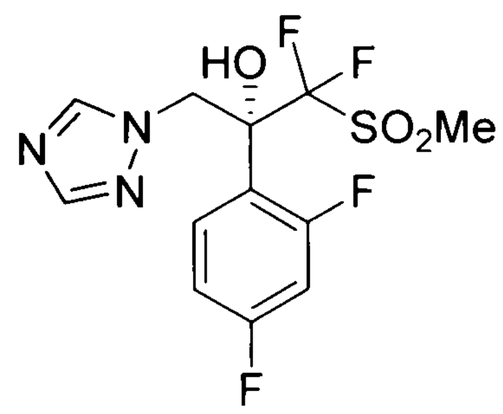
In the same journal publication, new 1,2,4-triazoles **157** were also presented as possessing high antifungal activity against yeasts.[80] Their structure is characterised by a difluoro(heteroaryl)methyl moiety, as depicted in Figure 11.



157

Figure 11

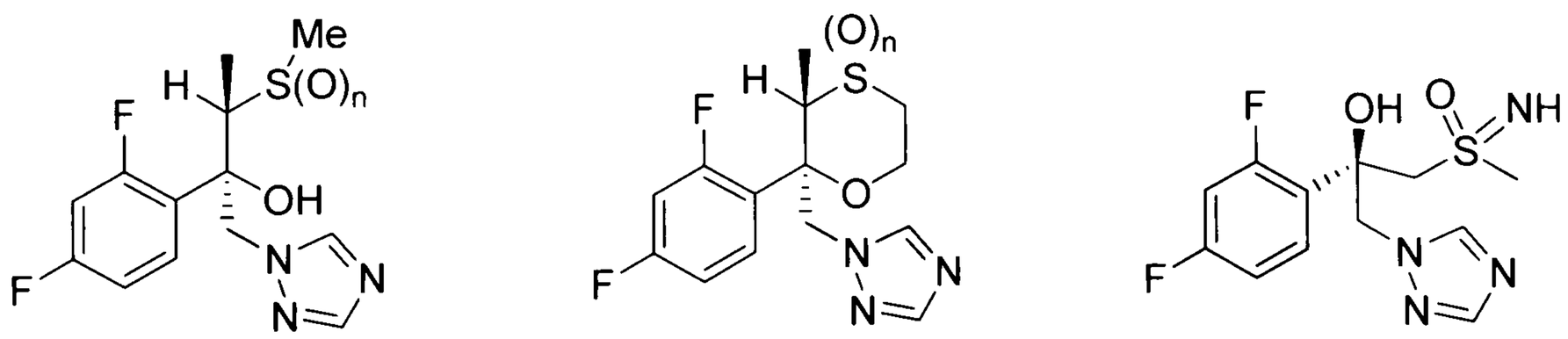
These studies have since been developed further and it has been demonstrated that the 1,2,4-triazole with the difluoro(substituted sulfonyl)methyl moiety **158** exhibit enhanced antifungal activity against *Candida*, *Aspergillus* (Figure 12).[81]



158

Figure 12

Other sulfur-derivatives (sulfides, sulfones and sulfoximines) have been designed and tested for antifungal activity and showed extremely potent antifungal activity (Figure 13).[82,83]



159 n= 0, 2 **160** **161**

Figure 13

Section 3.2: Aim of the project

The aim of this project was to develop a new class of 1,2,4-triazoles to test for antifungal activity. In the course of previous studies on the addition of sulfenic acids to dienes, to be outlined in greater detail in Section 3.3.1, the fragment 1,4-oxathiane-S-oxide was uncovered (Figure 14).

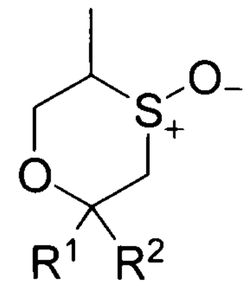
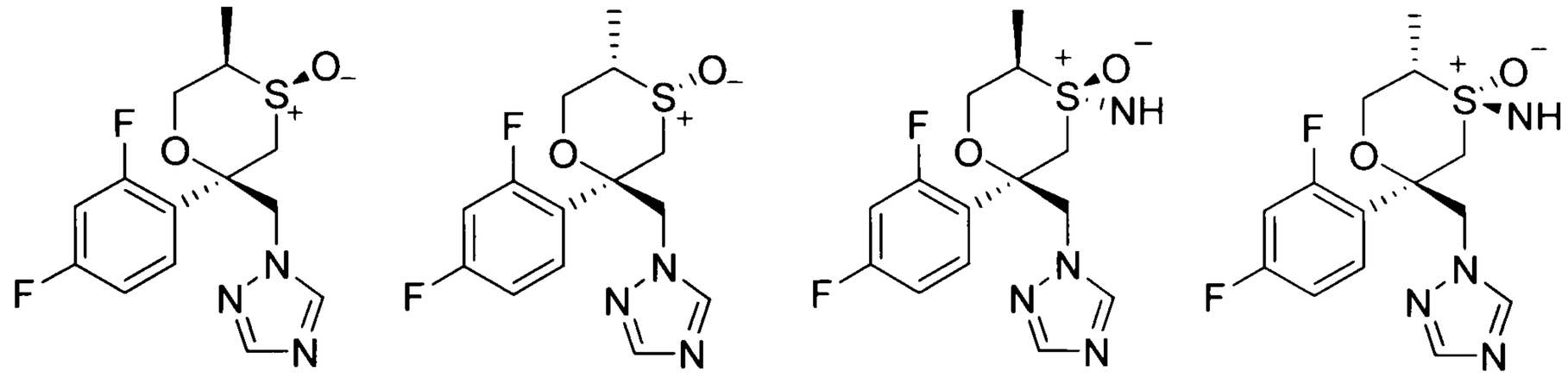


Figure 14

It was subsequently proposed to incorporate this structural motif into the synthesis of substituted 1,4-oxathiane-S-oxides **162-165** which would then be submitted for antifungal testing (Figure 15).



162 **163** **164** **165**

Figure 15

The 1,4-oxathiane-S-oxides are further composed of a 1,2,4-triazole unit and a difluoro-benzene ring. The compounds **164** and **165** are the corresponding sulfoximines of **162** and **163** respectively.

It was perceived that the 1,4-oxathiane-S-oxide functionality, like acetal moieties, would confer to the molecule a greater degree of hydrophilicity and hence make it more water-soluble than a simple hydrocarbon moiety. Therefore the compound should be delivered more easily to the target fungal enzyme. Furthermore, the sulfoxide functionality is

proposed to act as a polar moiety, like 1,2,4-triazole, to improve solubility and should enhance the activity against systemic infection. It is well documented that two fluorine atoms in the benzene ring enhances the antifungal activity,[84] as indeed the 1,2,4-triazole unit does. The extra nitrogen atom in sulfoximines **164** and **165** adds an additional donor functionality for binding with the enzyme substrate and is sufficiently basic to form salts and therefore enhance the solubility.[83] The methyl group at the 5-position of the 1,4-oxathiane-S-oxide ring mimics the 13α-methyl group of lanosterol, as the non-polar portion of the ring mimics the correspondingly non-polar steroidal portion of lanosterol (Scheme 99).[85]

A description of the synthesis of compounds **162-165** is outlined in Section 3.3.2.

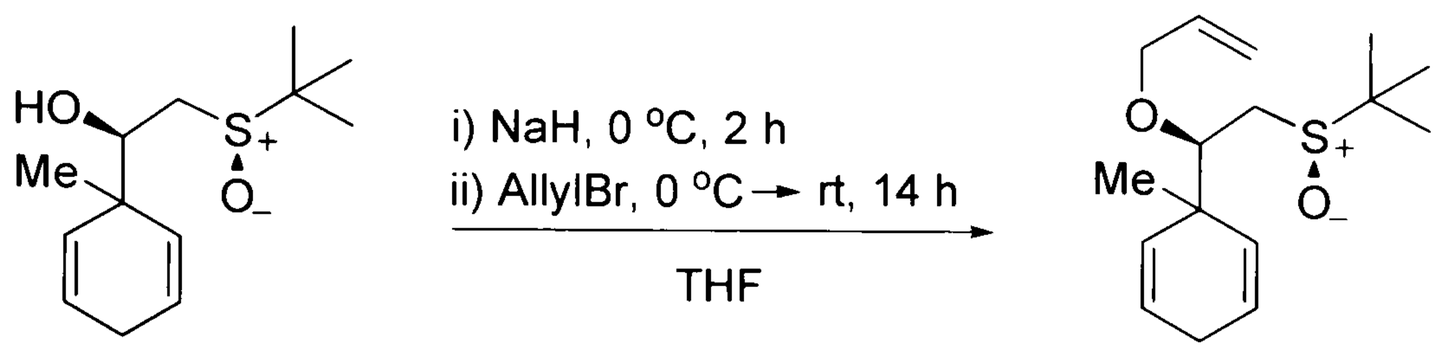
Section 3.3: Results and discussion

Section 3.3.1: Formation of the 1,4-oxathiane-S-oxide ring system

A novel synthesis of 1,4-oxathiane-S-oxide rings was discovered as a result of a serendipitous reaction.

In the attempt to gain further insight into the selectivity of the cyclisation for compound **83**, the free hydroxyl functionality was protected with a variety of different protecting groups (Chapter 2, Section 2.3, Table 2).

One of the examples included the protection of alcohol **83b** as an allyl ether, as shown in Scheme 101.

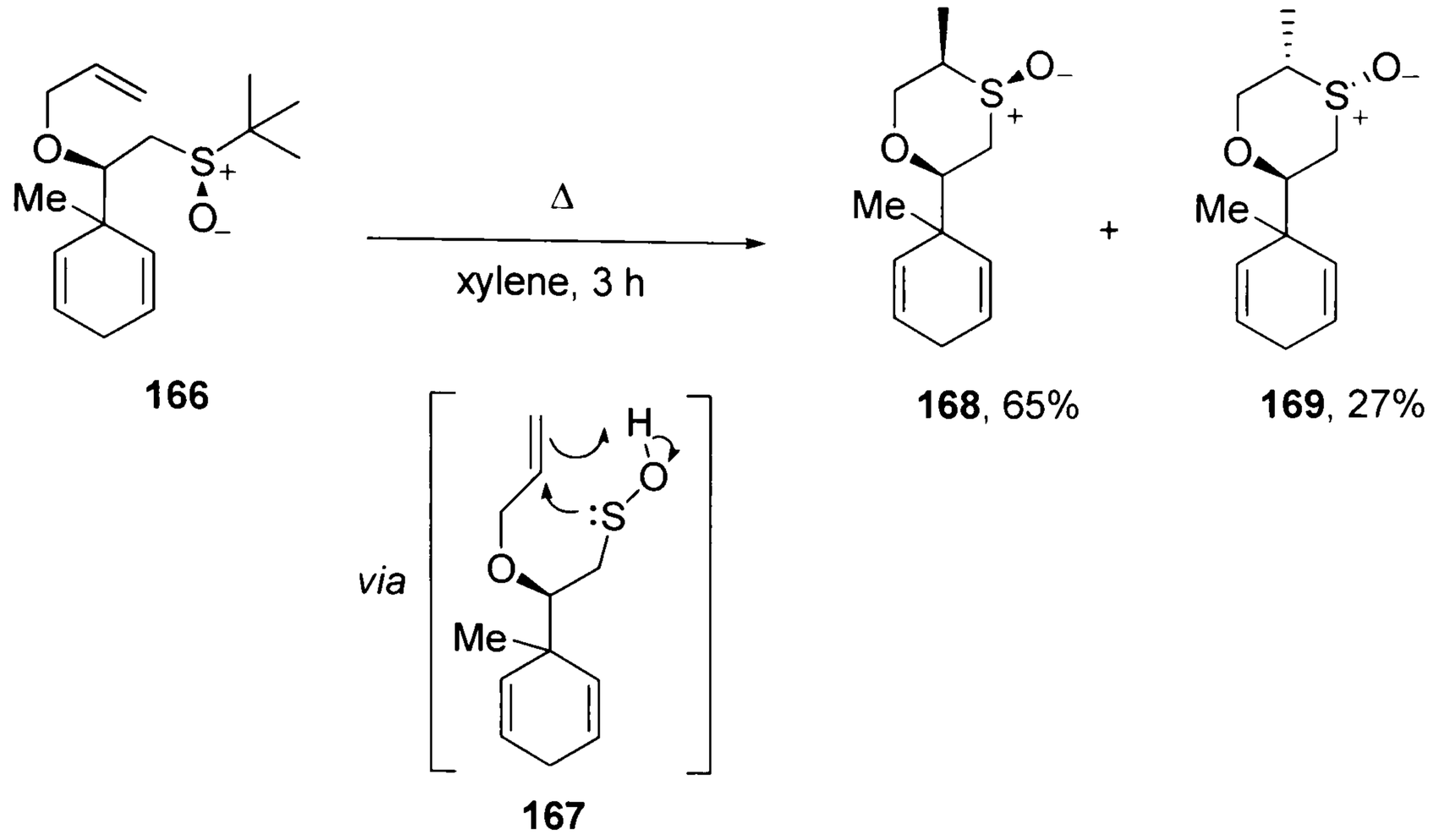


83b 84% **166**

Scheme 101

ß-Hydroxy sulfoxide **83b** was reacted with allyl bromide overnight before the reaction was subjected to a standard work-up procedure. The crude mixture was purified by column chromatography (diethyl ether) to afford the protected alcohol **166** as a pink oil in good yield. The novel compound was fully characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry and IR spectroscopy.

The sulfoxide **166** was then submitted to the standard thermolysis conditions (Scheme 102).



166 **168**, 65% **169**, 27%

167

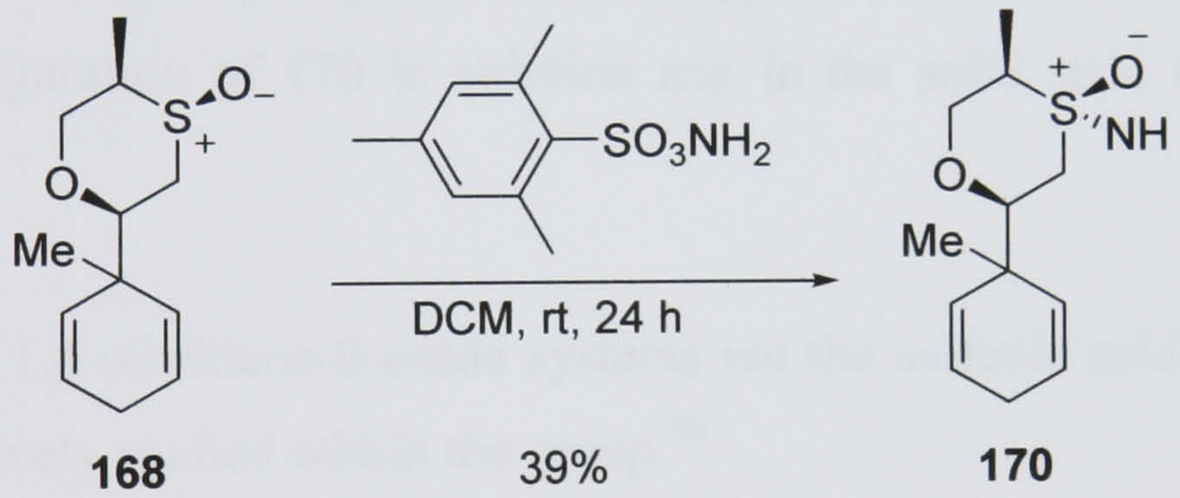
Scheme 102

After 3 hours at reflux in xylene, the reaction mixture was subjected to column chromatography (7:3 diethyl ether/60-80 °C petroleum ether) to afford two new cyclic sulfoxides. Analysis of the corresponding ^{1}H NMR spectra revealed the structures of the novel compounds **168** and **169** to be 1,4-oxathiane-S-oxides, which were independently isolated in a ratio of 2.4 to 1. The sulfenic acid intermediate **167** added chemo- and regioselectively to the allyl group forming the 1,4-oxathiane-S-oxides **168** and **169**, and none of the anticipated perhydrobenzothiophene S-oxide is formed, which would arise from addition to the diene (Chapter 2). For the geometrical requirements of the transition state for the addition of a sulfenic acid to an alkene (i.e. coplanarity of the 5 participating atoms), the relative stereochemistry between the sulfoxide and the methyl group is proposed to be *cis*, as shown in Scheme 102, and by analogy with Jones system (Scheme 5). Sulfoxides **168** and **169** differ in the relative stereochemistry between the sulfoxide and the carbon which connects the oxygen and the diene functionality. The novel compounds were subjected to full characterisation. Analysis of ^{1}H NMR spectra of compounds **168** and **169** revealed a high coupling constant (11.3 Hz) for the hydrogen α to the oxygen in **168**, and this would suggest its axial position in the oxathiane ring. It is known from calculations that the favoured conformation of 1,4-oxathiane-S-oxide systems is a chair with the sulfoxide locked in the axial position.[86] As a consequence of

the anisotropic effect of the sulfoxide, the hydrogen axial to the sulfoxide in **168** is shifted to downfield compared to the same hydrogen in **169**. Therefore these analyses would propose the configuration of **168** as shown in Scheme 102. However, it was felt necessary to prove these conclusions.

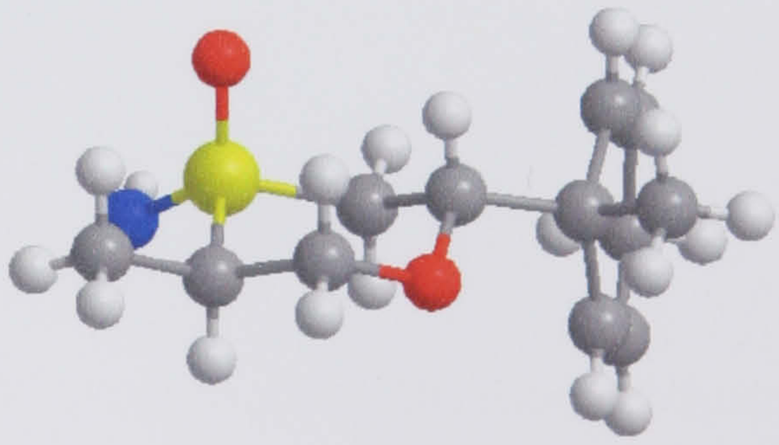
It was next thought to derivatise one of the compounds **168** or **169** to an alternative substrate which would hopefully give suitable crystals for X-ray crystal structure determination. The functionality in **168** and **169** that seemed appealing to manipulate for derivatisation was the sulfoxide. It is known that sulfoxides can be converted to the corresponding sulfoximines, which are often crystalline compounds, and that the reaction occurs with retention of stereochemistry at the sulfur atom.[87]

The major diastereoisomer **168** was therefore converted to the corresponding sulfoximine **170** (Scheme 103).[88]



168 39% **170**

Scheme 103



170

Figure 16

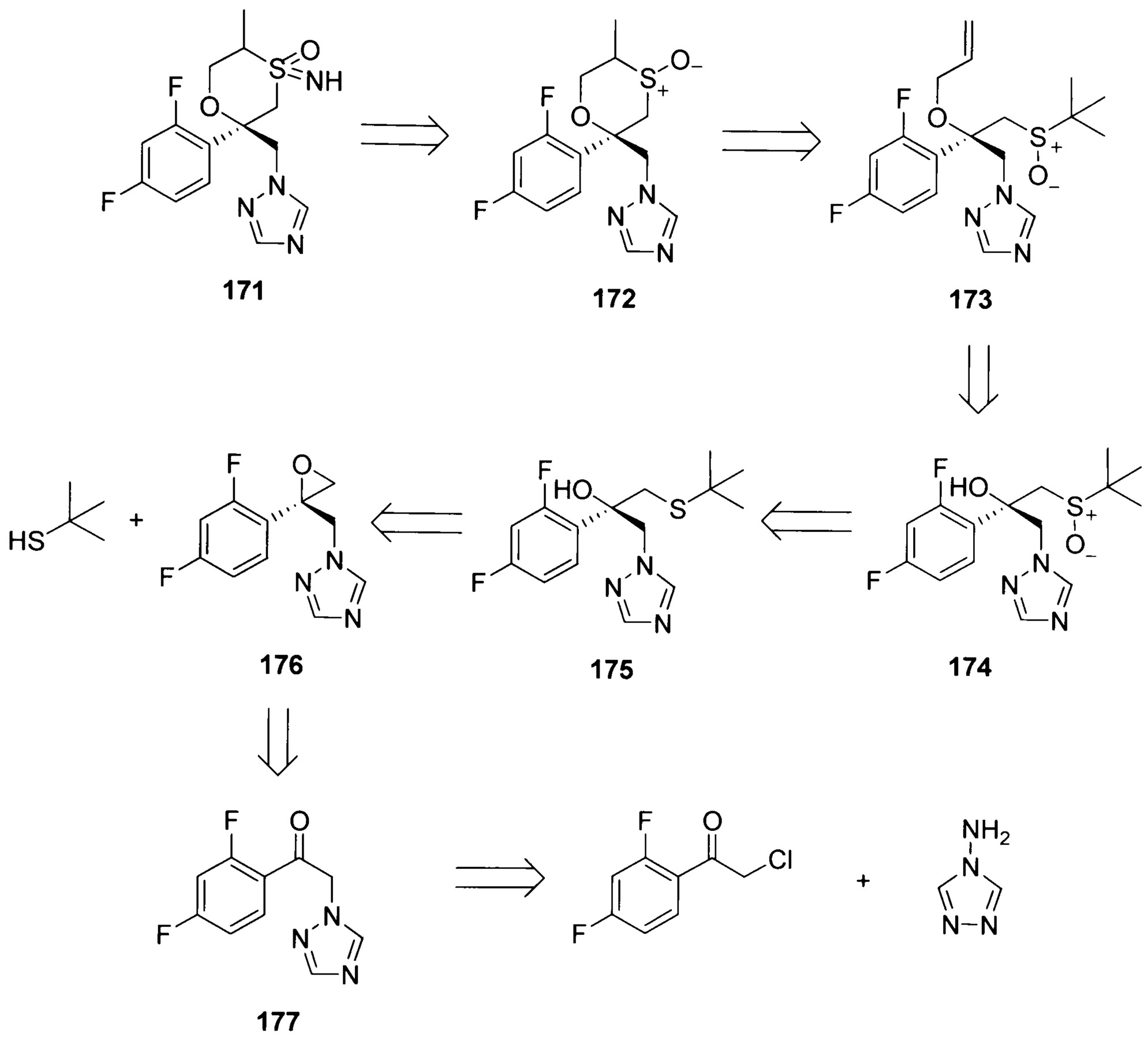
The sulfoxide **168** was stirred with crystalline *O*-mesitylsulfonylhydroxylamine (MSH) in dichloromethane at room temperature for 24 hours, before being subjected to work-up. MSH was prepared fresh following a two-step literature procedure,[89] starting from commercially available mesitylenesulfonyl chloride and ethyl-N-hydroxyacetimidate. After work-up **170** was isolated in 39% yield as a white solid with 38% of recovered starting material. The desired sulfoximine afforded a suitable crystal for analysis proceeding slow evaporation of the solvent ethyl acetate.

Crystallographic analysis determined unambiguously the configuration of **170**, and consequently of the sulfoxide **168** (Figure 16 and Appendix 6.6). The crystallographic analysis showed also that the 1,4-oxathiane-S-oxide fragment sits in a well-defined chair conformation, with the methyl group in an equatorial position, and *cis* to the oxygen of the sulfoximine, which sits axial. Analysis of ^{1}H NMR spectrum of **170** revealed a high coupling constant (11.4 Hz) of one hydrogen of the CH_2 α to the sulfur suggesting a diaxial coupling with the hydrogen α to the oxygen. Therefore these analyses would propose the configuration of **170** in solution and in the solid state to be as shown in Scheme 103.

The formation of 1,4-oxathiane-S-oxide systems *via* the sulfenic acid cycloaddition has since been extensively studied within the group.[90]

Section 3.3.2: Synthesis of new potential antifungal agents

One possible retrosynthesis outline for the potential antifungal agents is depicted in Scheme 104.

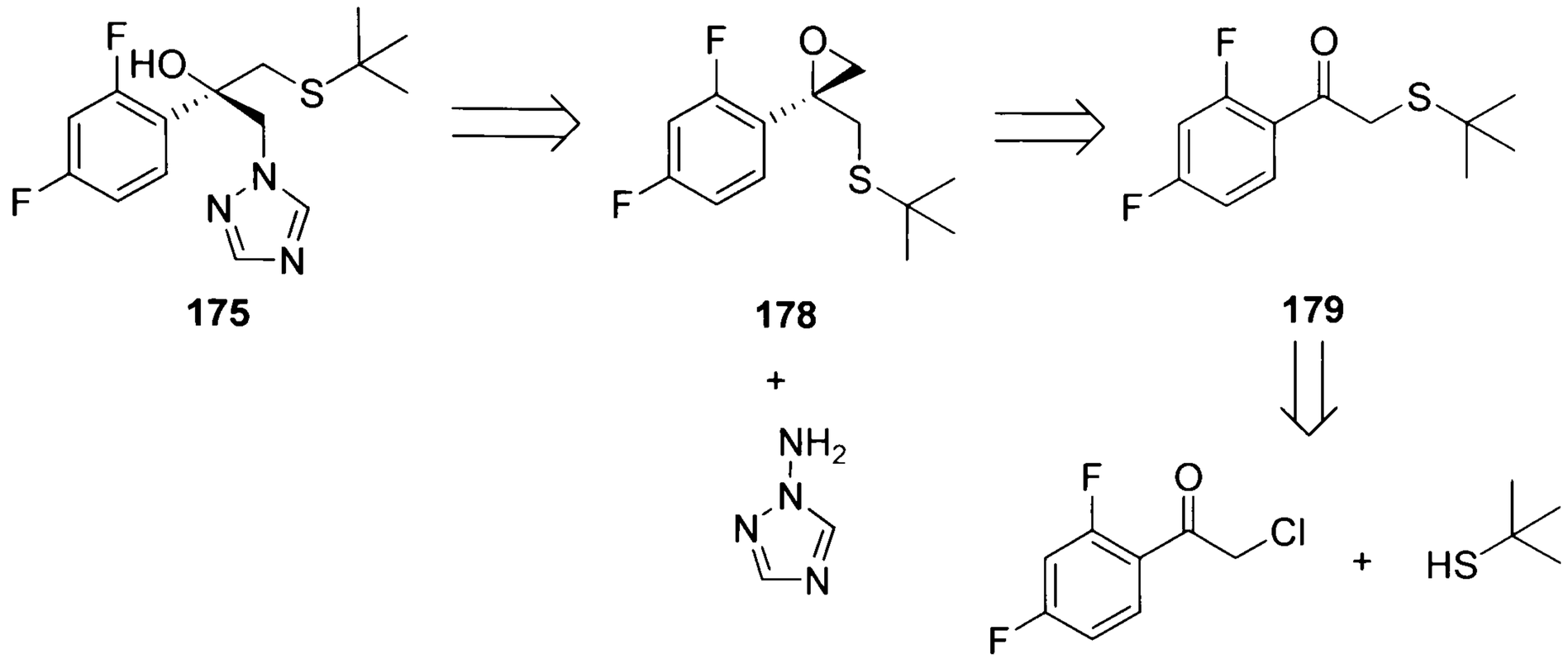


Scheme 104

The sulfoximine **171** could derive from sulfoxide **172**, which is the cyclisation product of allyl ether **173**. The protected hydroxyl derivative **173** could in turn come from alcohol **174**. The sulfoxide **174** could derive from oxidation of sulfide **175** which is the product of condensation between commercially available *t*-butyl thiol and epoxide **176**. The epoxide **176** can be made from the ketone **177**, which comes from the condensation of two

commercially available materials, 2-chloro-2`,4`-difluoro acetophenone and 4-amino-1,2,4-triazole.

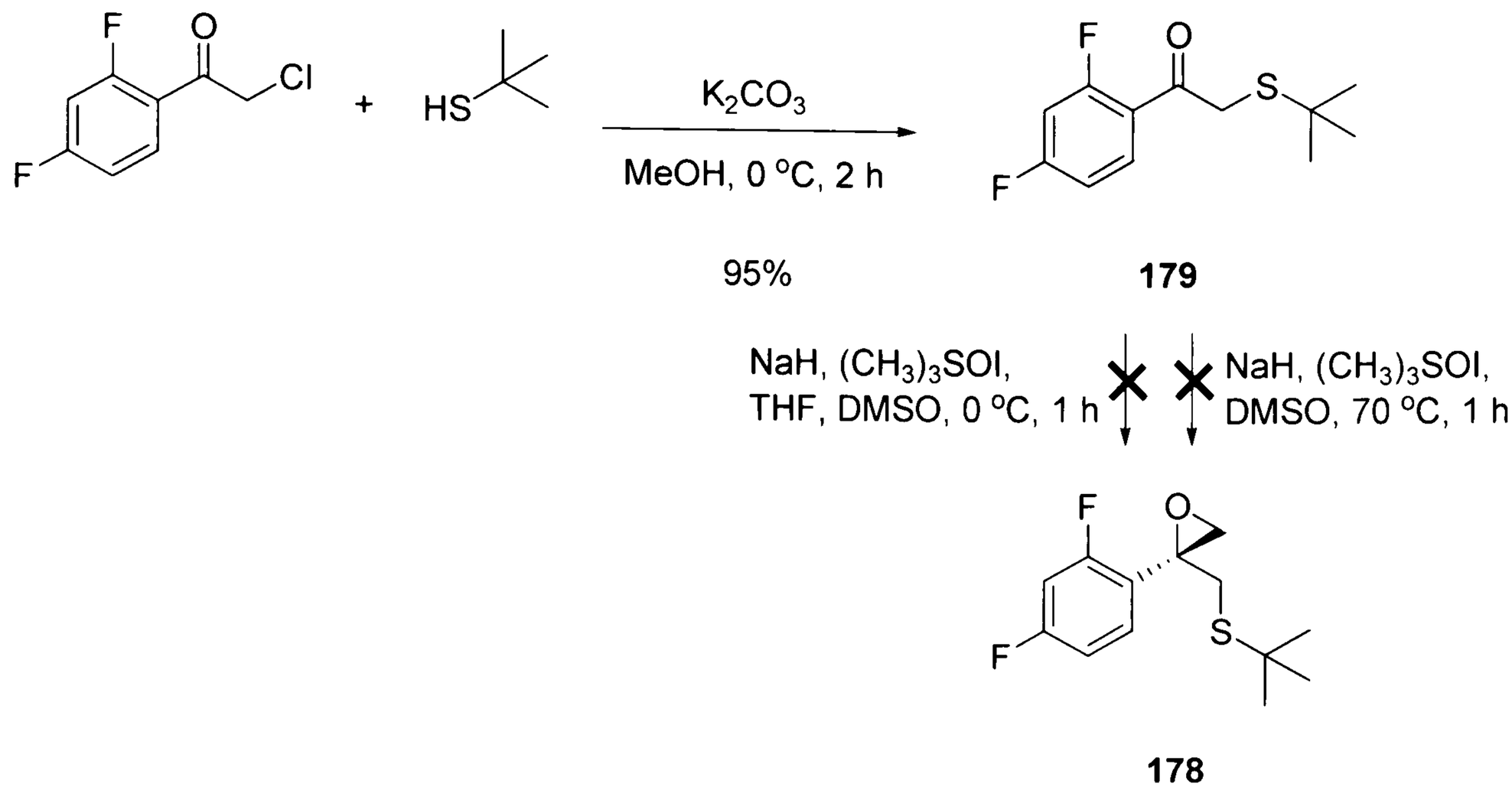
An alternative approach to **175** that was proposed is oulined in Scheme 105.



Scheme 105

Alcohol **175** could be made by opening of epoxide **178** with commercially available 1,2,4-triazole-1-ylamine. The epoxide could derive from ketone **179**, the product of condensation between *t*-butyl thiol and 2-chloro-2`,4`-difluoro acetophenone.

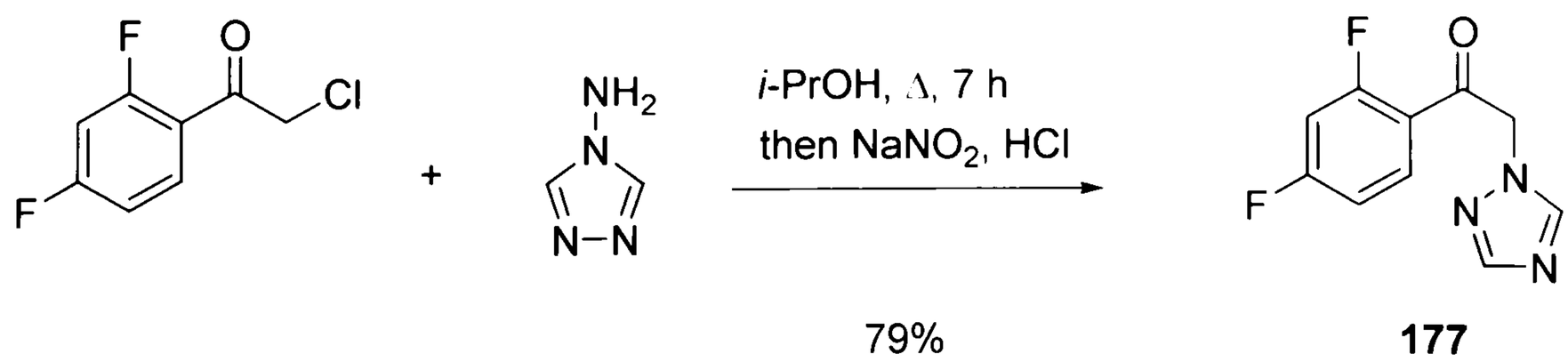
The synthesis of ß-keto sulfide **179** was accomplished following a literature procedure (Scheme 106).[91]



Scheme 106

The product **179** was isolated in excellent yield and carried through to the next stage of the synthesis. The approach failed in the synthesis of epoxide **178** and therefore the strategy outlined in Scheme 104 was employed.

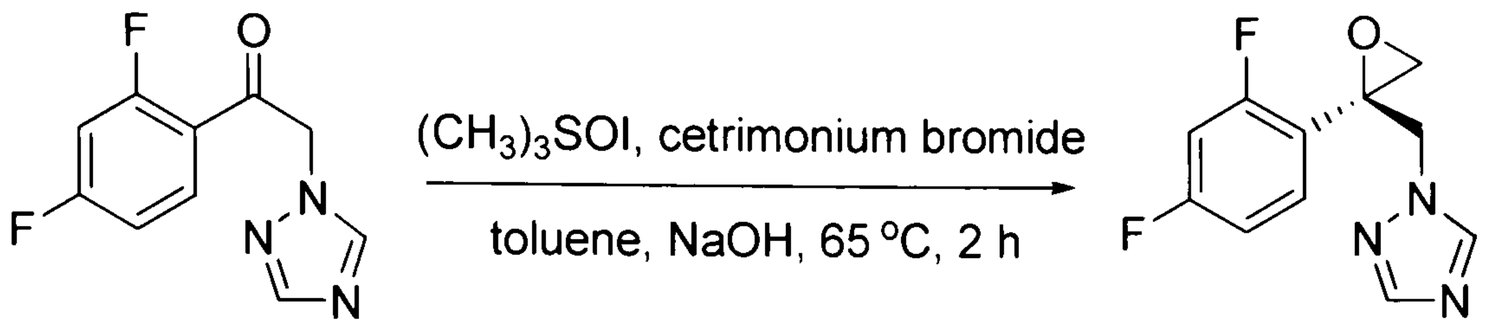
For the synthesis of ketone **177** a standard literature procedure was followed (Scheme 107).[92]



Scheme 107

After work-up the ketone **177** was isolated as a fine yellow powder and it was carried through to the next step without further purification.

After several unsuccessful attempts,[66,93] ketone **177** was finally converted to epoxide **176**, as shown in Scheme 108.[94]

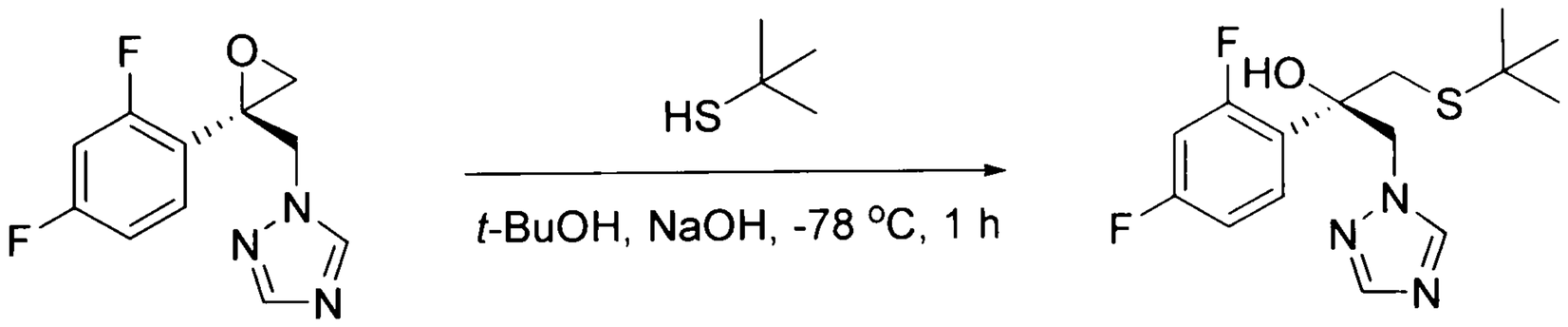


177 57% **176**

Scheme 108

Ketone **177** was stirred with trimethylsulfoxonium iodide, NaOH and cetrimonium bromide in toluene for 2 hours at 65 °C, before being subjected to a standard work-up procedure. Purification by column chromatography (5% Et_3N in diethyl ether) afforded epoxide **176** as a pale yellow oil. Et_3N is added to the eluent to avoid possible ring-opening of the epoxide on the acidic silica column. The novel compound was fully characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry and IR spectroscopy.

The epoxide **176** was then regioselectively opened with *t*-butyl thiol (Scheme 109).[95]

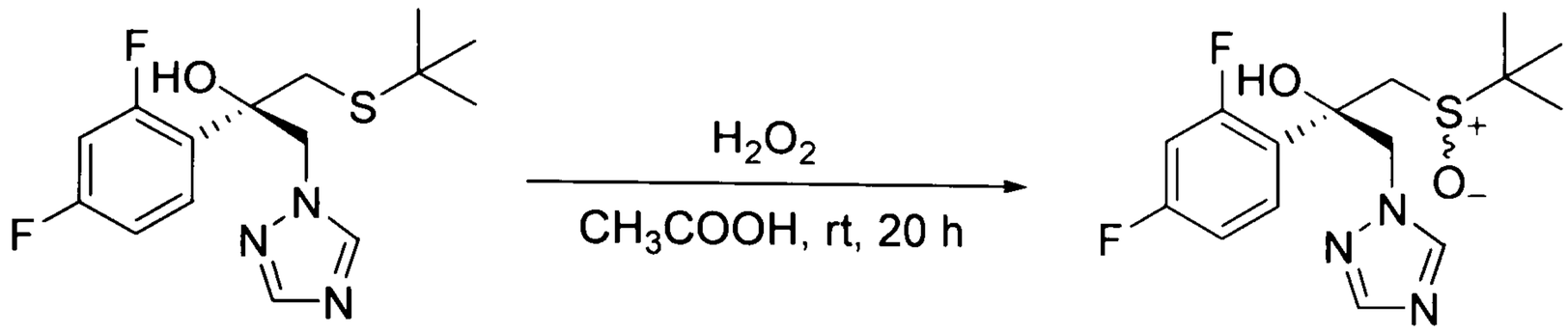


176 90% **175**

Scheme 109

The epoxide **176**, in *t*-butyl alcohol and NaOH at -78 °C, was reacted with *t*-butyl thiol. The reaction mixture was left to stir for a further 20 minutes at -78 °C before being subjected to a standard work-up to afford alcohol **175** as a white solid. The novel compound was fully characterised and deemed pure enough to be carried through to the next step of the synthesis without further purification.

The sulfide **175** was converted to the sulfoxide as shown in Scheme 110.[48]

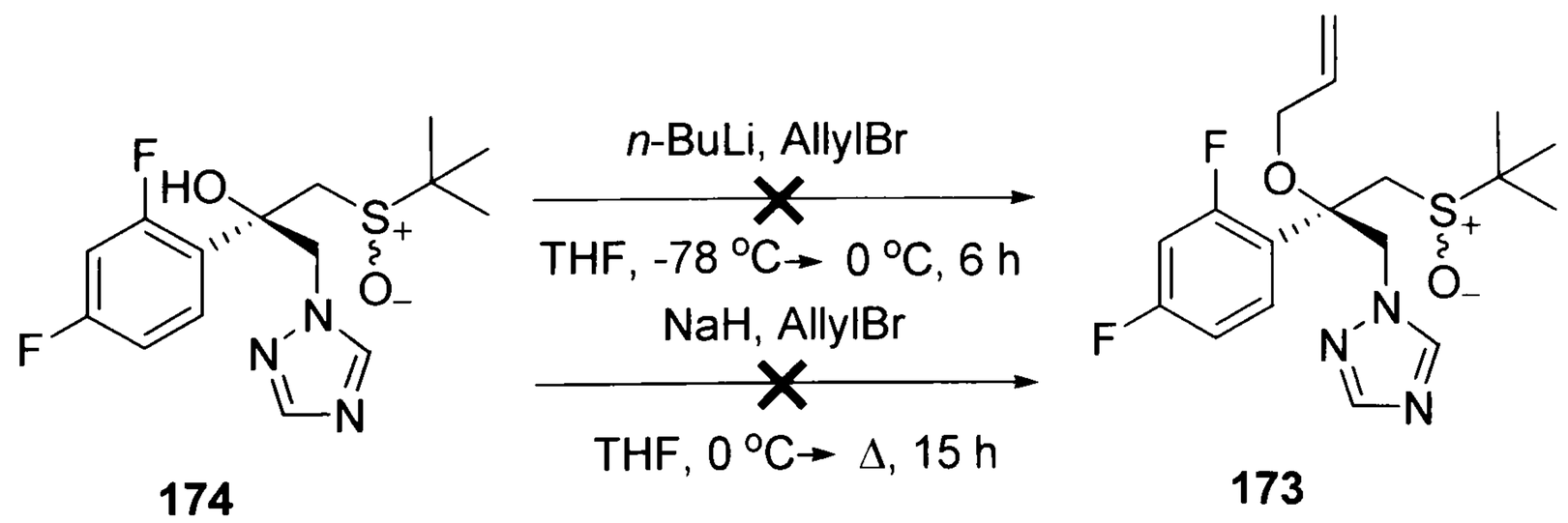


175 80% (dr 6:1) **174**

Scheme 110

Sulfide **175** was left to stir with a 27% hydrogen peroxide solution overnight before being subjected to standard work-up conditions to afford the sulfoxide **174** as a white solid in good yield. By ^{1}H NMR analysis **174** is present as a mixture of two diastereoisomers in a ratio of 6 to 1. The novel mixture of diastereoisomers was fully characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry, IR spectroscopy and melting point analysis. The relative configuration of major and minor diastereoisomer was not determined.

Attempts to protect the free hydroxyl functionality with allyl bromide to obtain sulfoxide **173** proved unsuccessful (Scheme 111).

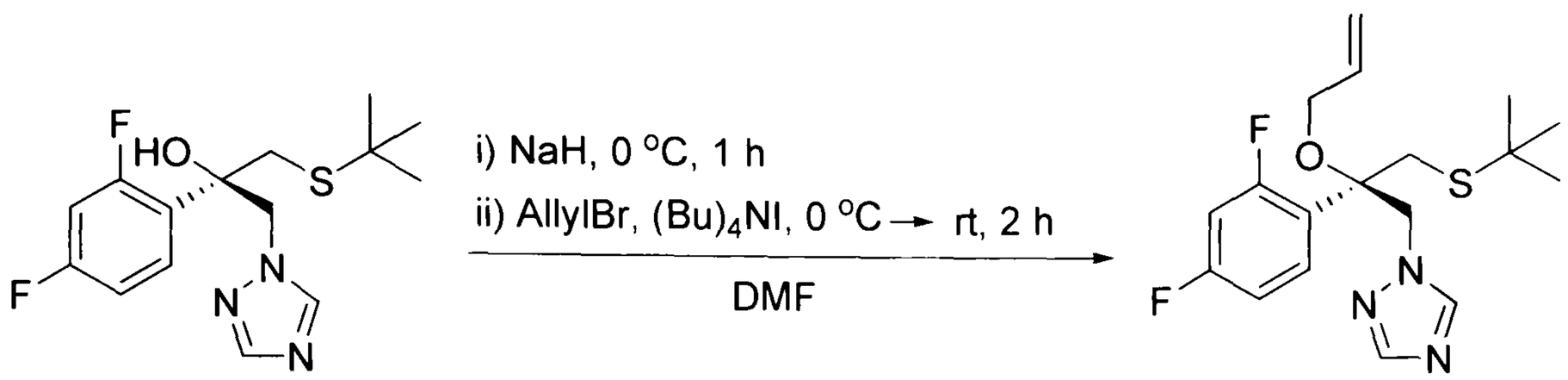


174 **173**

Scheme 111

It was next thought to first protect the alcohol moiety in **175** and then convert the corresponding sulfide functionality to the sulfoxide.

Alcohol **175** was protected as its corresponding allyl ether (Scheme 112).[96]

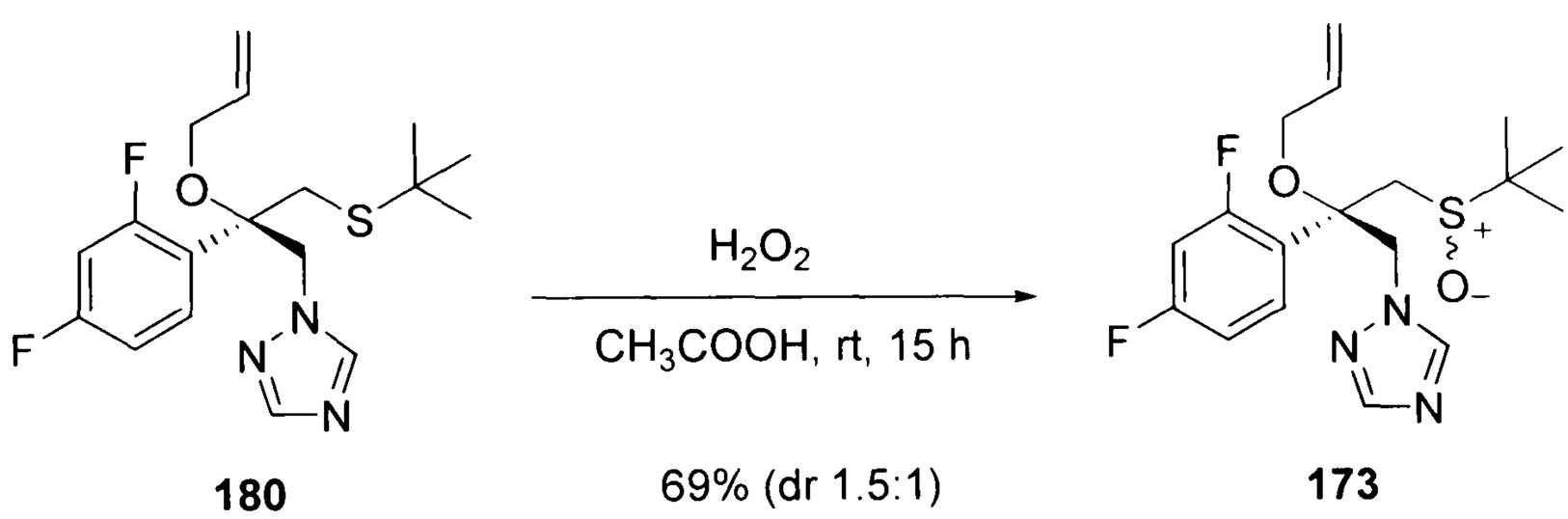


175 92% **180**

Scheme 112

Alcohol **175** was reacted with allyl bromide for 2 hours before being subjected to a standard work-up that gave compound **180** in excellent yield. The novel compound was deemed pure enough to not require further purification, by ^1H NMR spectra analysis.

The sulfide **180** was then converted to the sulfoxide (Scheme 113).

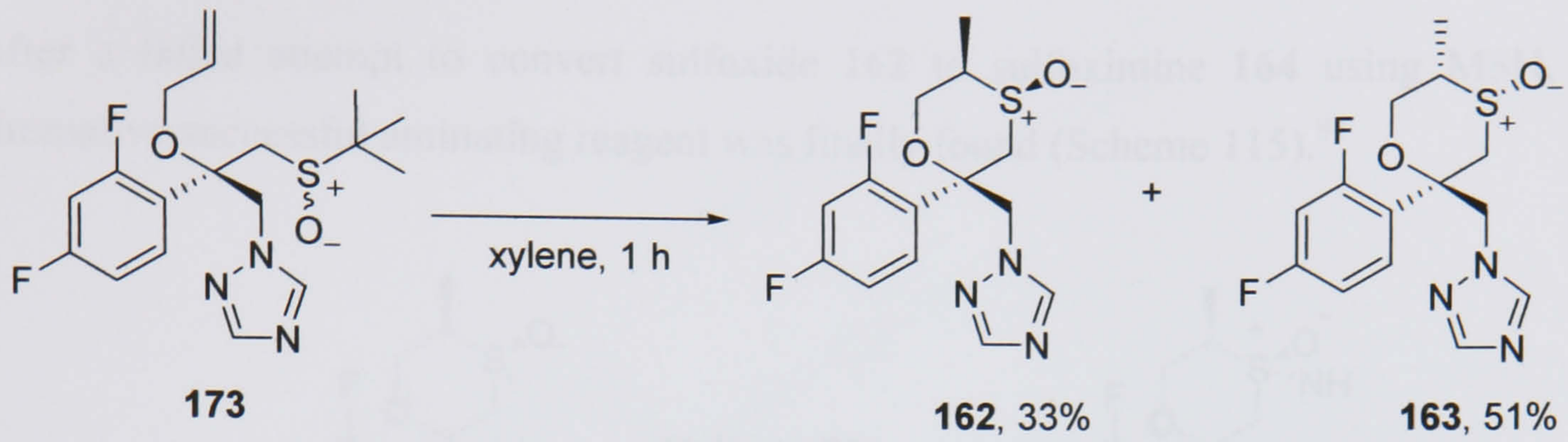


180 69% (dr 1.5:1) **173**

Scheme 113

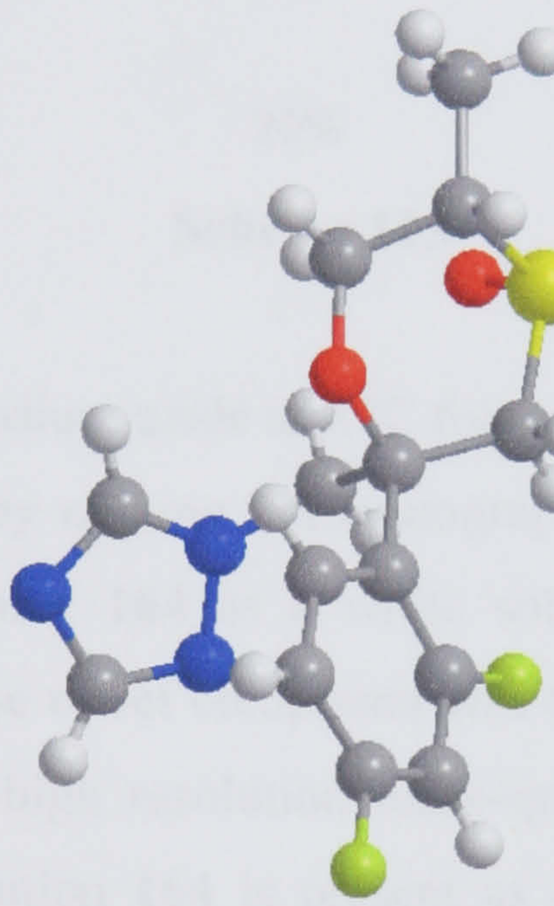
The reaction was left to stir overnight before being subjected to work-up. Purification by column chromatography (5:95 methanol/diethyl ether) afforded sulfoxide **173** in good yield and as a mixture of inseparable diastereoisomers in a ratio of 1.5 to 1. The mixture was characterised by ^1H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry and IR spectroscopy.

The sulfoxide **173** was then submitted to standard thermolysis conditions, as shown in Scheme 114.



173 **162**, 33% **163**, 51%

Scheme 114



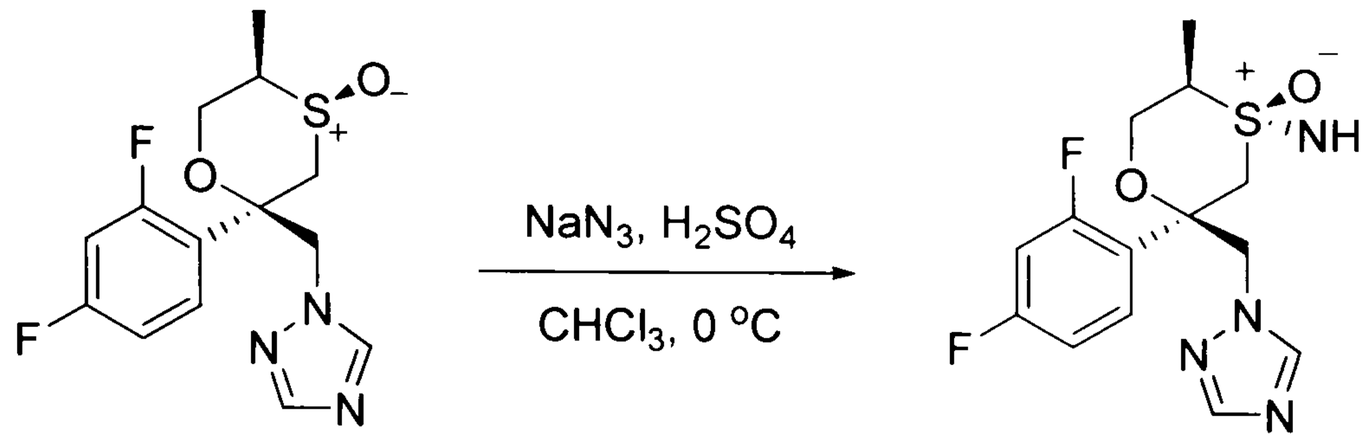
162

Figure 17

Compound **173** was left to reflux for 1 hour before the reaction mixture was subjected to column chromatography (2:8 methanol/diethyl ether), which afforded the cyclic sulfoxides **162** and **163** as white solids in a ratio of 1 to 1.5 respectively. Compound **162** gratifyingly afforded a suitable crystal, after slow evaporation of the solvent dichloromethane, for X-ray crystallographic analysis (Figure 17 and Appendix 6.7). This determined unambiguously the configuration of **162** and consequently of **163**. In the solid state **162** sits in a chair conformation where the sulfoxide functionality is axial and the aromatic ring equatorial on the oxathiane ring. The one conformation of **162** present in

solution is identical to that found in the solid state, based on ^{1}H NMR analysis. The novel compounds were extensively characterised.

After a failed attempt to convert sulfoxide **162** to sulfoximine **164** using MSH, an alternative successful aminating reagent was finally found (Scheme 115).[97]

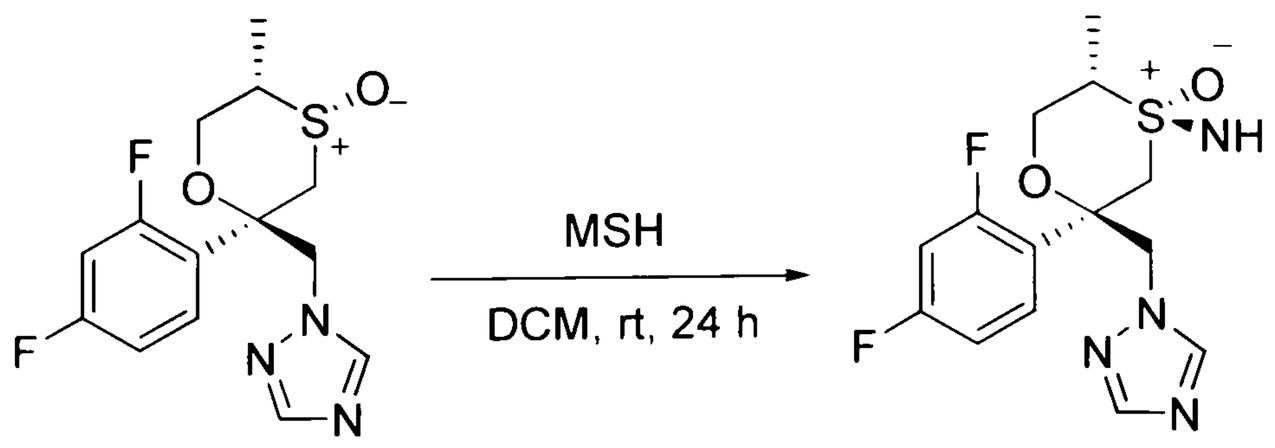


162 20% **164**

Scheme 115

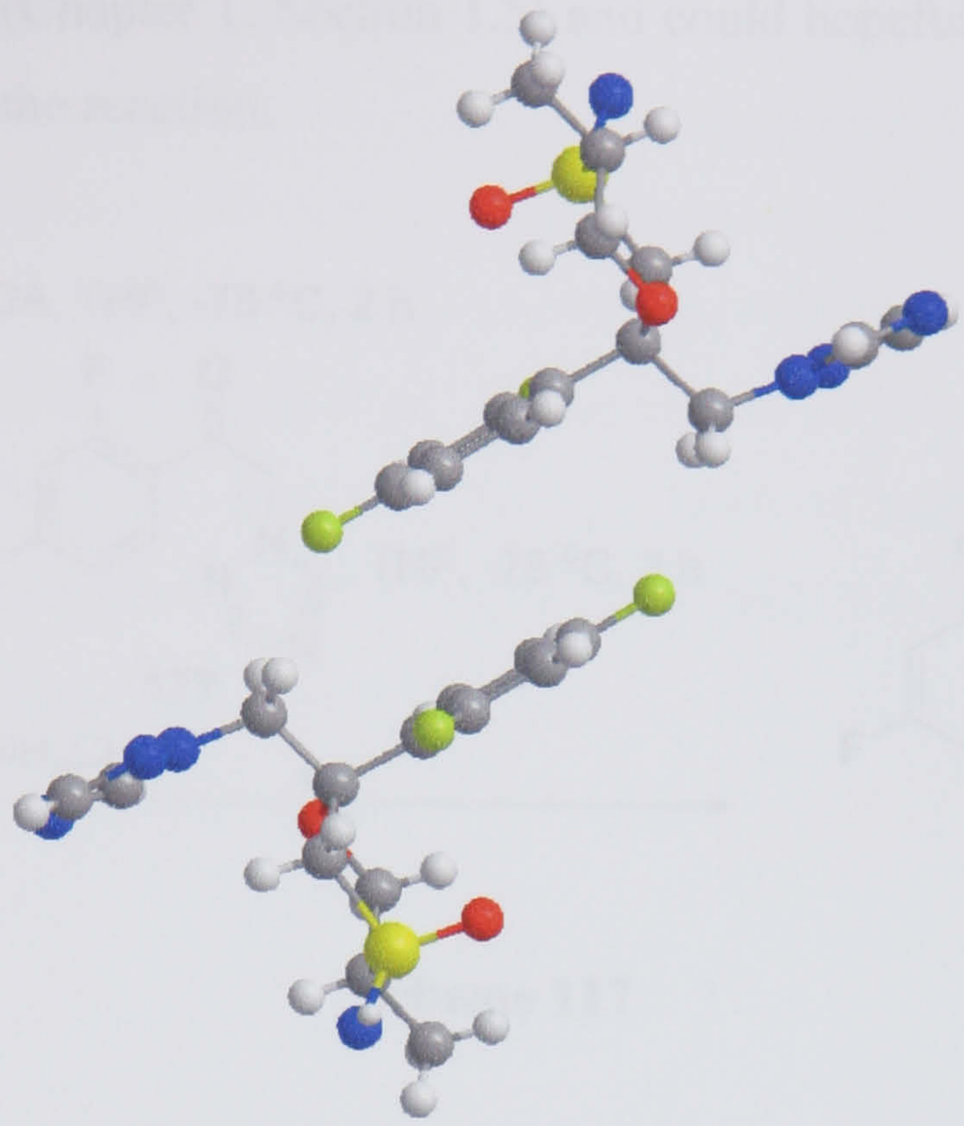
To sulfoxide **162** was added sodium azide at 0 °C followed by H_2SO_4, before the reaction was worked-up. Purification by column chromatography (4:96 methanol/diethyl ether) afforded the desired sulfoximine **164** as a white solid and the recovery of 37% of unreacted starting material. The novel compound was fully characterised by ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry, IR spectroscopy and melting point analysis. In solution **164** is present as only one conformation, with the methyl group equatorial.

Substrate **163** was consequently derivatised to sulfoximine **165** (Scheme 116).[88]



163 41% **165**

Scheme 116



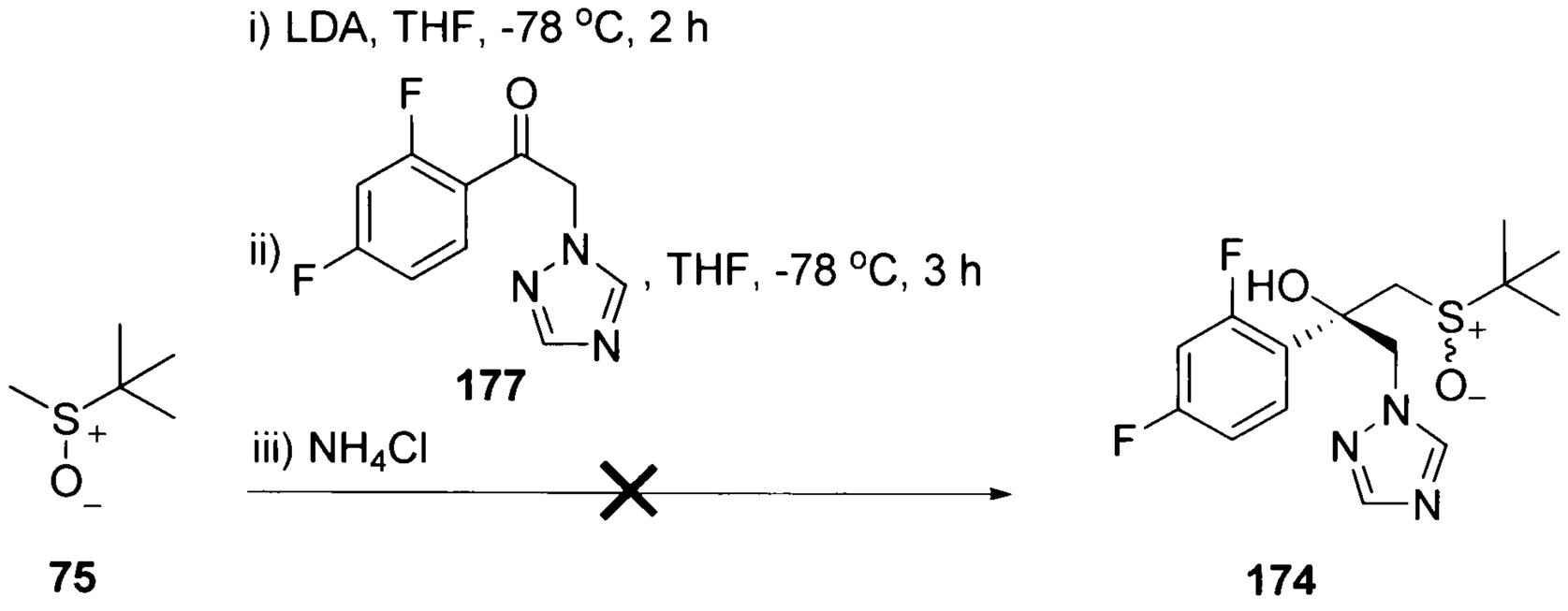
165

Figure 18

The sulfoxide was stirred with *O*-mesitylsulfonylhydroxylamine for one day before being worked-up. Purification by column chromatography (2:8 methanol/diethyl ether) afforded sulfoximine **165** in moderate yield as a white solid and the recovery of 36% of unreacted starting material. A suitable crystal of compound **165** was also isolated for X-ray crystallographic analysis, after slow evaporation of the solvent dichloromethane (Figure 18 and Appendix 6.8). The compound **165** crystallises in a conformation where the oxygen of the sulfoxide functionality sits axial in the chair of the oxathiane ring, and the benzene rings in the dimer sit face-to-face. The conformation of **165** in the liquid state is identical to that of the solid state, based on ^{1}H NMR analysis. The novel compound **165** was submitted for full characterisation.

To examine the feasibility of synthesising **162-165** enantiomerically pure, the synthesis of alcohol **174** was initially attempted from the condensation of racemic *t*-butyl methyl sulfoxide **75** and ketone **177** (Scheme 117). *t*-Butyl methyl sulfoxide can be prepared

enantiomerically pure (Chapter 1, Section 1.5) and could hopefully be used to introduce enantioselectivity into the reaction.



Scheme 117

The anion of *t*-butyl methyl sulfoxide was left to react with ketone **177** for 3 hours before the reaction was subjected to standard work-up. ^{1}H NMR spectra analysis of the crude reaction mixture revealed the presence of unreacted starting materials.

It would therefore appear that this approach to control the stereochemistry of the quaternary alcohol using a chiral relay with *t*-butyl methyl sulfoxide is not a viable one. An alternative route to the synthesis of **162-165** in enantiomerically pure form would be to treat alcohol **175** to kinetic or enzymatic resolution, strategies that have not been attempted but merit further investigation. An alternative strategy would be to test on ketone **177** the conditions recently published for the synthesis of terminal epoxides enantiomerically pure *via* sulfonium methylene transfer.[98] Goodman *et al* reported the successful results of this reaction for a range of substituted aromatic aldehydes.

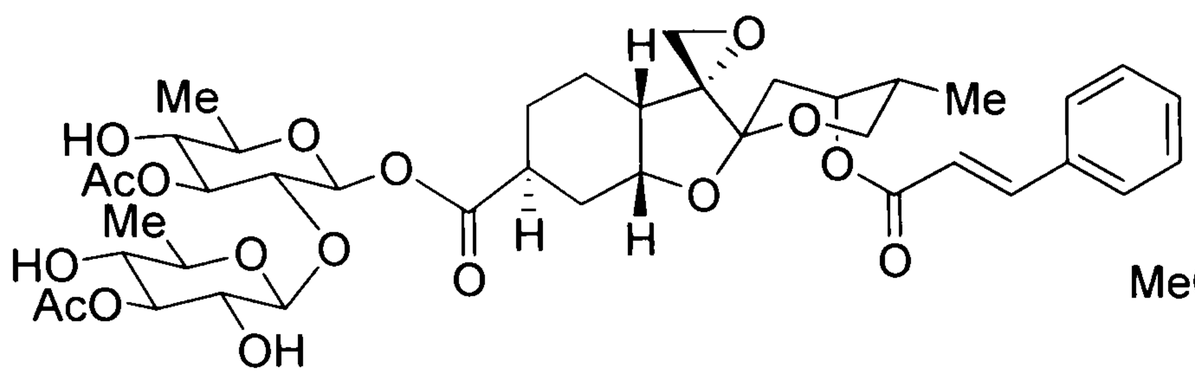
Section 3.4: Summary

In this chapter a new protocol for the synthesis of 1,4-oxathiane 4-oxide systems has been presented. The serendipitous discovery of this new methodology was made during a course of study on the intramolecular cycloaddition reaction of sulfenic acids with dienes: in this instance the addition preferentially occurred onto an allyl functionality (Section 3.3.2). The protocol has been applied to the synthesis of potential antifungal agents (Section 3.3.3) incorporating a 1,2,4-triazole unit and 2,4-difluorobenzene ring as substituents on the 1,4-oxathiane ring system.

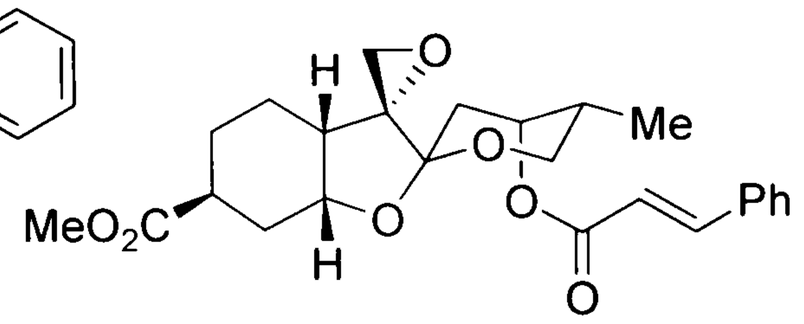
Chapter 4

Section 4.1: Introduction and background

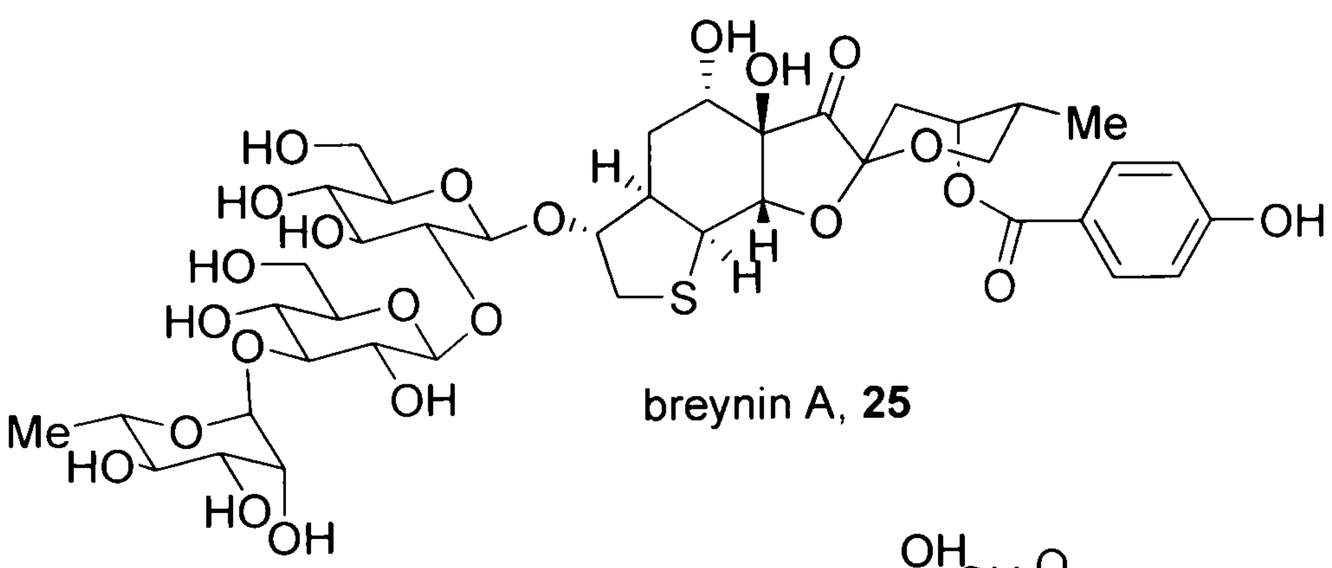
Phyllanthoside **181** is a spiroketal glycoside natural product which is a potent inhibitor of several NCI tumor cell lines, including human breast cancer. The corresponding aglycon hydrolysis product phyllanthocin **27**, that is biologically inactive, has attracted considerable attention from the scientific community and a number of total syntheses have appeared in the literature.[18] Similar in structure to phyllanthoside **181** and to the aglycone phyllanthocin **27**, are breynin A **25** and breynolide **28** respectively, which have previously been described in Chapter 1, Section 1.3. Most recently phyllaemblic acid **182** and the methyl ester of phyllaemblic acid **183**, which comprise the norbisabolane skeleton, have been isolated (Figure 19).[99]



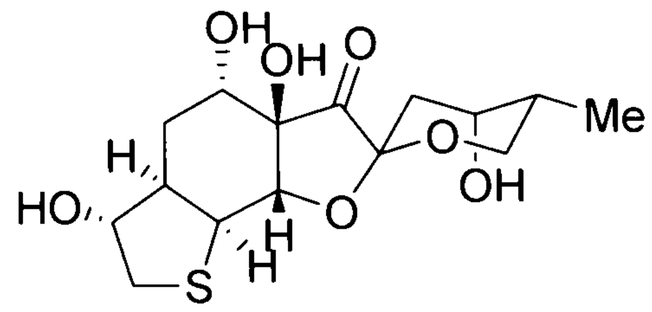
phyllanthoside, **181**



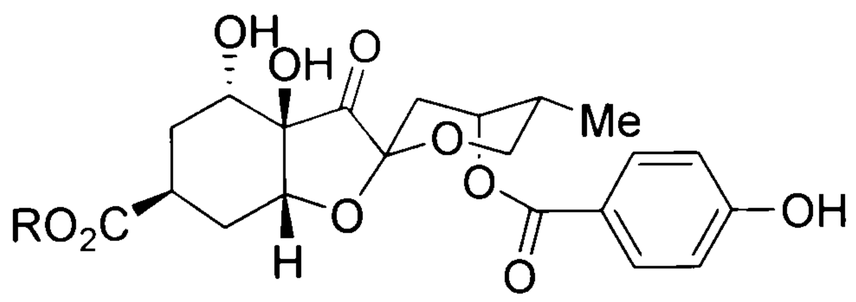
phyllanthocin, **27**



breynin A, **25**



breynolide, **28**



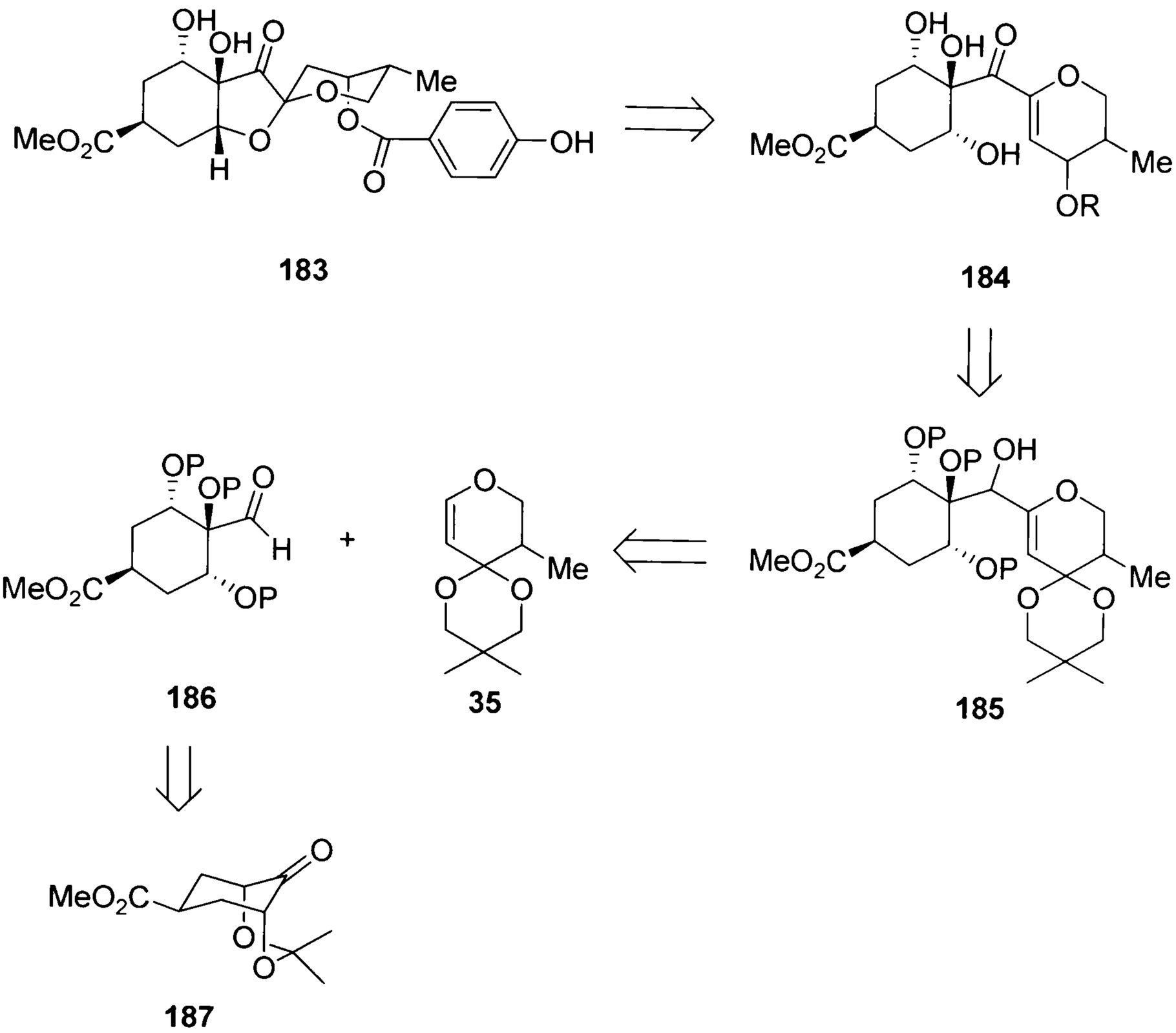
R=H phyllaemblic acid, **182**
R=Me methyl ester of phyllaemblic acid, **183**

Figure 19

Section 4.2: Aim of the project

The aim of this project was to devise a synthetic route to the highly challenging oxygenated cyclohexane core of the aforementioned natural products with particular attention to the still synthetically unexplored phyllaemblic acid **182** and its methyl ester **183**.

Key to the approach is the recognition of a latent symmetry element in the carbocyclic portion of the natural product, which can be more clearly seen after disconnection of the spirocyclic acetal moiety. The proposed retrosynthetic outline, *vide infra*, employs new methodology for the synthesis of **187**. One way in which **187** could be employed in a synthesis of the natural product is through conversion to **186**, which can in turn be coupled with **35**[100] to give the spiroketal functionality of **183**. From herein, existing literature methodology used for the racemic synthesis of breynolide **28**[14a] and phyllanthoside **181**[100] can be employed *en route* to the target molecule (Scheme 118).



183 184 186 35 185 187

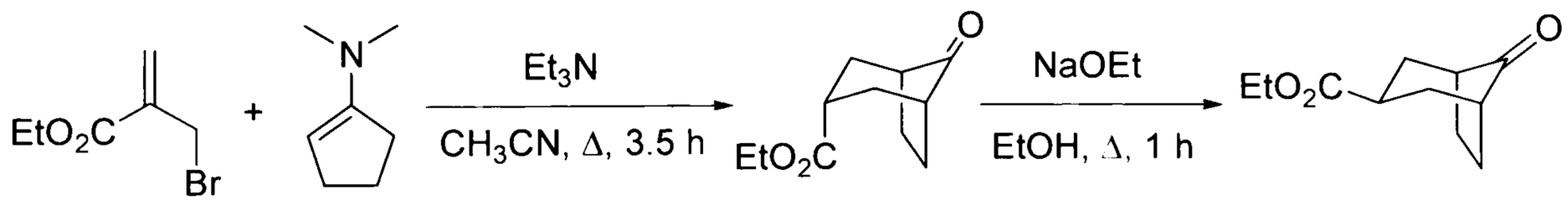
Scheme 118

The idea was to employ the racemic dihydropyran **35**, used by Smith *et al* for the synthesis of the spiroketal portion of phyllanthocin and breynolide, in a coupling reaction with aldehyde **186** to furnish the substrate **185**, which can in turn be manipulated for the synthesis of the natural product **183**. The conditions, used by Smith *et al*, potentially set the spirocentre (if the "correct" stereocentre is engaged) and the stereochemistry of the methyl group in the pyranone ring. The stereogenicity of the ester-protected alcohol in **183** will be set by substrate control. A novel approach to the synthesis of aldehyde **186** was therefore required. The aldehyde **186** could be obtained *via* a one carbon homologation of ketone **187**. It was anticipated that substrate control could be used to dictate the conversion of **187** to **186**. Therefore, the entire stereochemical issue for the synthesis of **186** and hence **183**, is reduced to the preparation of **187** possessing the configuration shown. In theory, the same approach could be applied to the synthesis of

phyllanthocin **27** and breynolide **28**. The starting meso compound **187** contains the *cis* relative stereochemistry between the protected hydroxy groups in **186** and the symmetry elements of **186**, which are still present in the carbocyclic core of **183**. Of particular interest in such an approach is whether the equilibrating conditions used by Smith *et al* selectively give the spiroketal present in the natural product. If this is the case, questions still remain to be answered: how are the hydroxy groups in **184** differentiated to give the spiroketal of the natural product **183** and why is the one formed the more thermodynamically stable?

An asymmetric route to the natural product can also be envisaged employing non-racemic chiral **35** as a coupling partner for **186**, if the strategy outlined in Scheme 118 is successful.

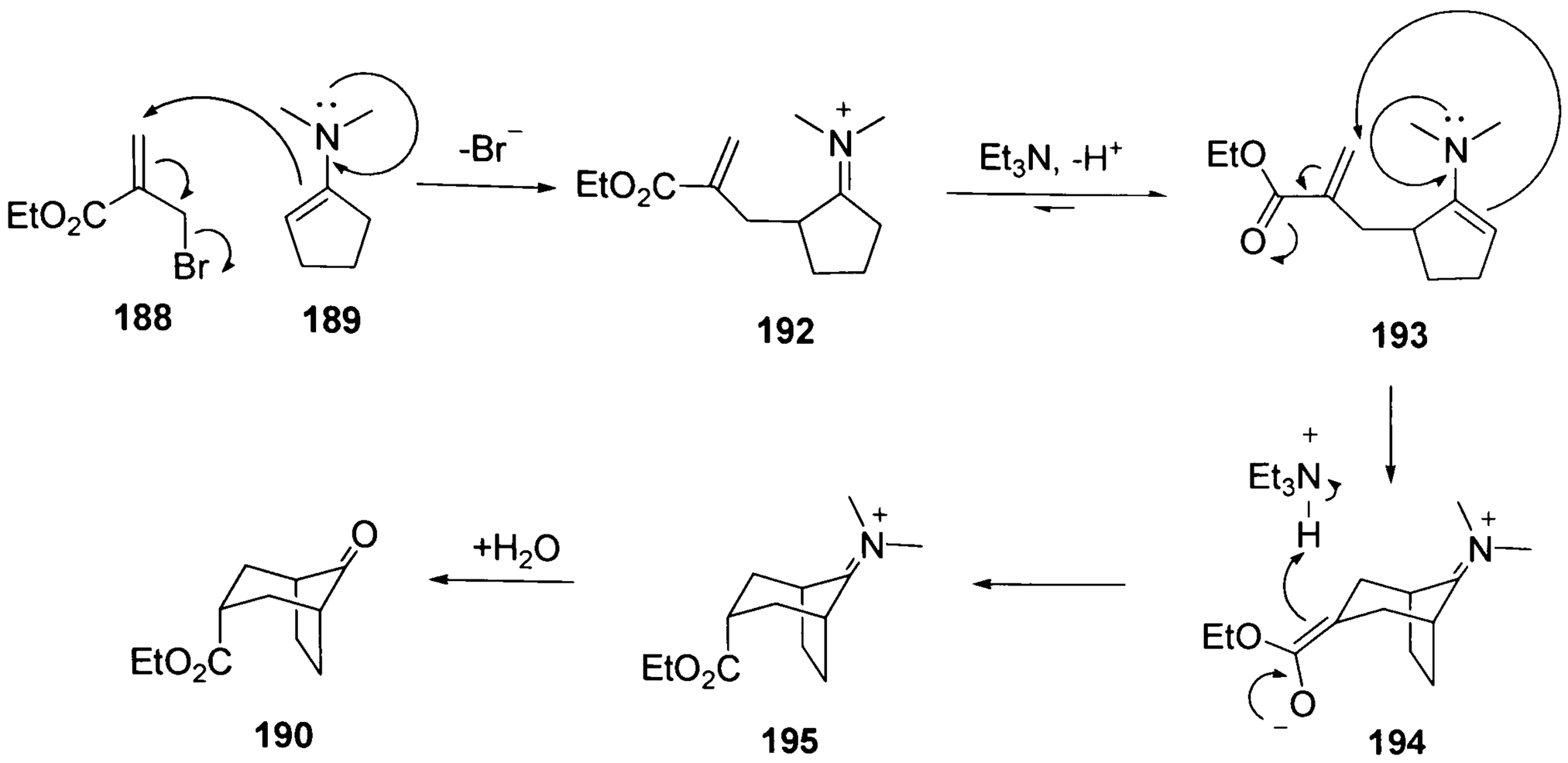
An old literature publication inspired the synthesis of methyl ester **187**. Lawton and coworkers reported the synthesis of *exo*-[3.2.1]-bicyclooctanone **191**, which was accomplished by a facile epimerisation of the *endo* keto ester **190**.[101] The keto ester **190** is the result of an annelation reaction between ethyl α-(1-bromomethyl)acrylate **188** and cyclopentanone enamine **189** (Scheme 119).



188 **189** 80% **190** 75% **191**

Scheme 119

Ester **191** is the product of a sequence of C-alkylation, tautomerisation and a Michael reaction between the enamine **189** and the bis-electrophile **188**; which serves sequentially as both an alkylation and a Michael addition reagent (Scheme 120).

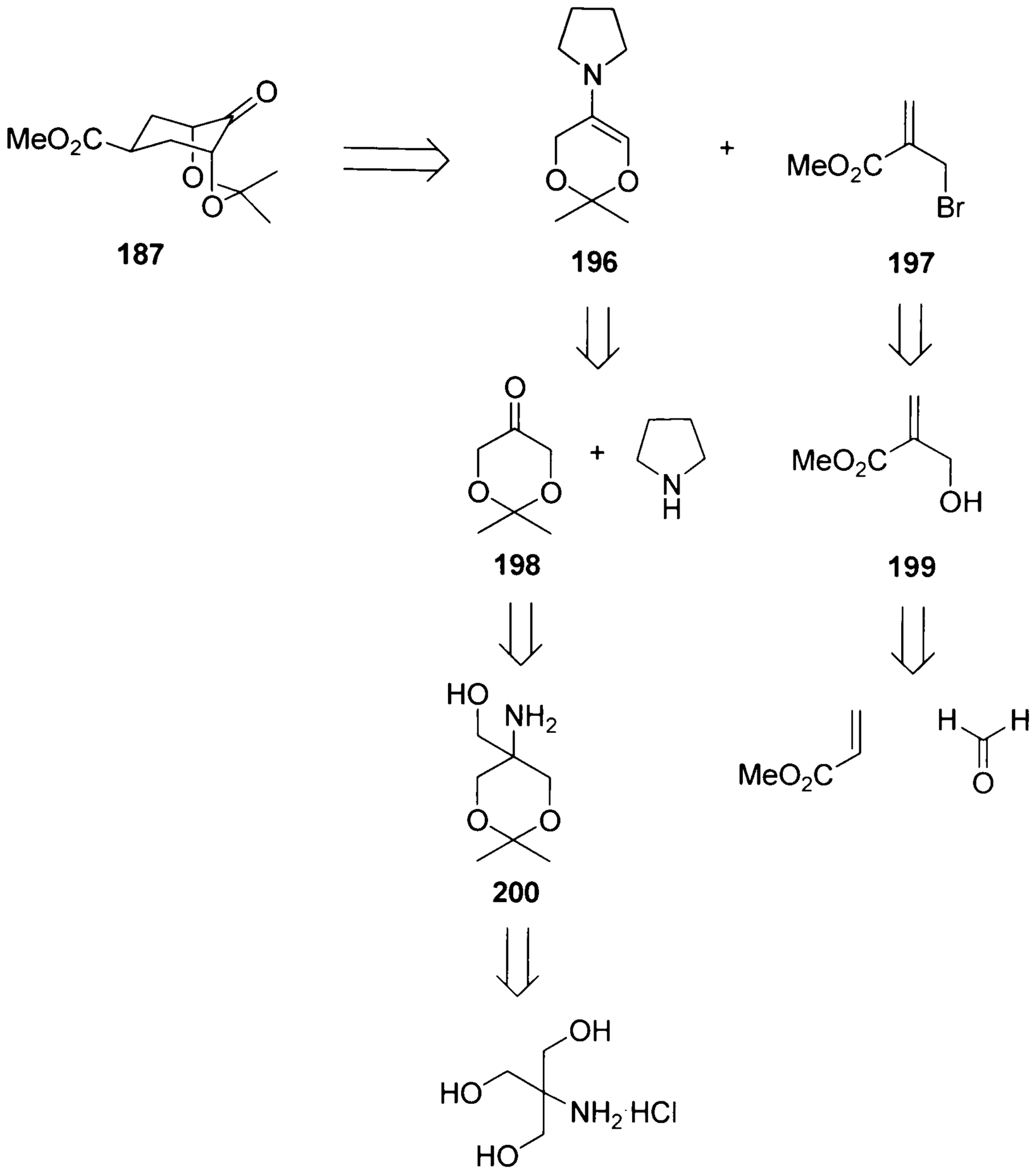


Scheme 120

Triethylamine is necessary to assist tautomerisation of **192** to the enamine **193** which can then undergo conjugate addition. The salt then re-protonates the enolate **194**. The resulting stereochemistry is due to the chair-like conformation of the developed ring assumed in the Michael stage of the reaction and protonation of the formed enolate **194** occurring from the least hindered side of the molecule.

Since the original publication in 1966 this methodology has been applied to the construction of a number of cyclic structures in a single step.[102]

The idea was to construct the ketoester **187** via the α,α'-annelation reaction between enamine **196** and allyl bromide **197** as outlined in Scheme 121.

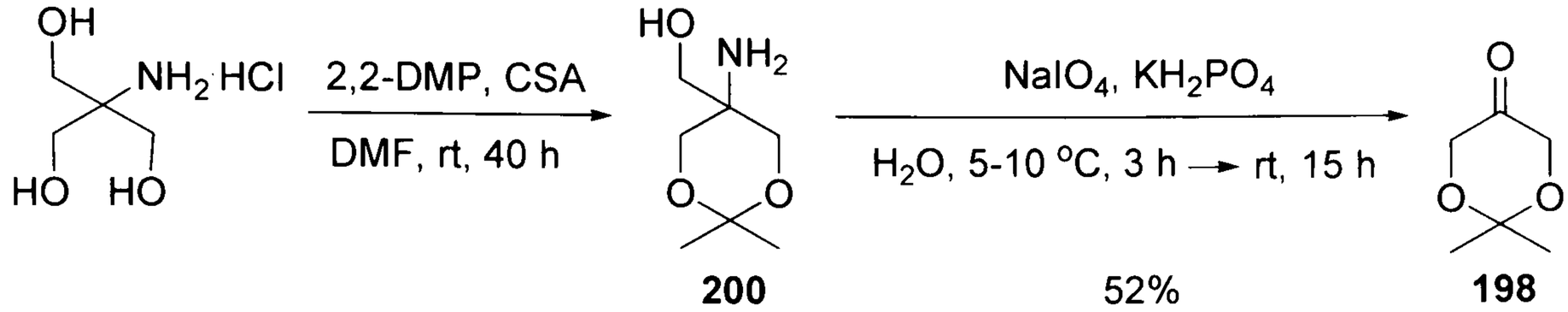


Scheme 121

The enamine **196** could be prepared from the corresponding ketone **198** and pyrrolidine. Dioxanone **198** could be made following a two step literature procedure starting from commercially available 2-amino-2-hydroxymethyl-1,3-propandiol hydrochloride.[103] The allyl bromide **197** could come from the corresponding alcohol **199**, which is the product of a Baylis-Hillman condensation between paraformaldehyde and methyl acrylate.

Section 4.3: Results and discussion

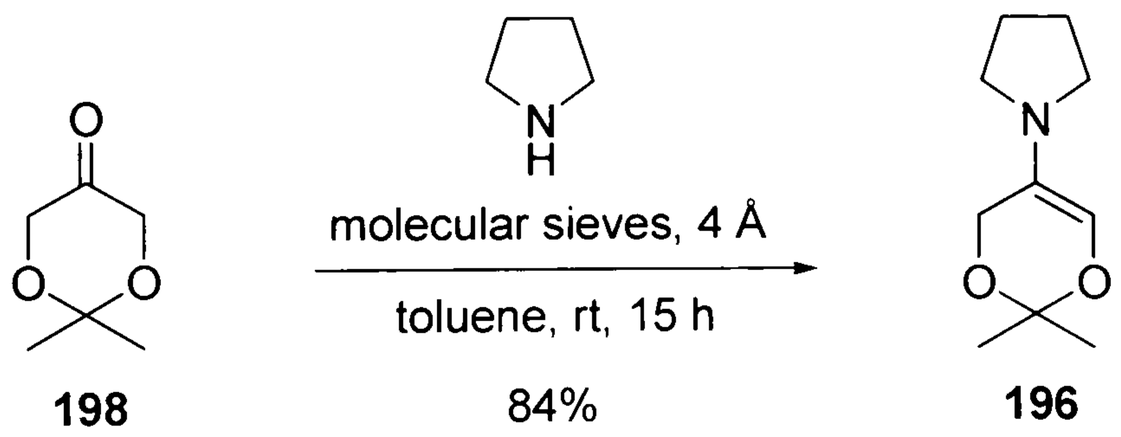
2-Amino-2-hydroxymethyl-1,3-propandiol hydrochloride was subjected to a two-step literature procedure to give 2,2-dimethyl-1,3-dioxane-5-one **198** as depicted in Scheme 122.



Scheme 122

The preparation of **198** started from the aminotriol and followed a modified procedure by Woodward and Vorbrüggen reported by Hoppe *et al.*[104] and later used by Enders *et al.*[103] 2,2-Dimethyl-1,3-dioxane-5-one **198** was isolated and purified by distillation (bp 50-54 °C/11 Torr) to afford a colourless oil in 52% yield over two step (lit.[103] 58%).

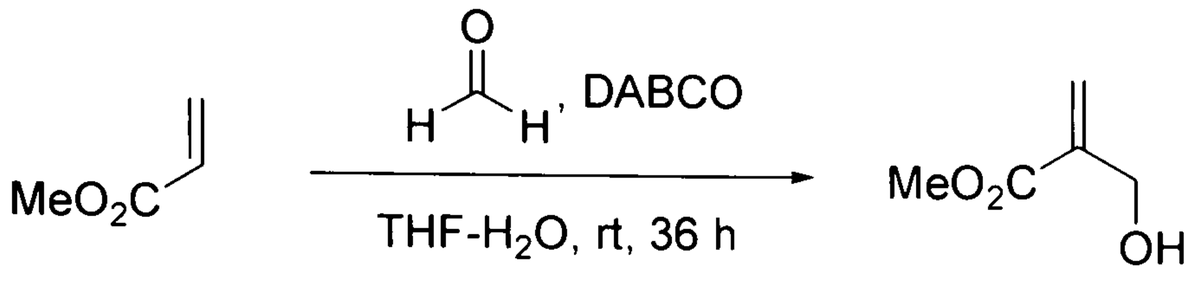
The ketone **198** was next derivatised to its corresponding enamine **196** (Scheme 123).[105]



Scheme 123

2,2-Dimethyl-1,3-dioxane-5-one **198** was stirred overnight with pyrrolidine before being worked-up to give the novel enamine **196** in excellent yield and without the need for further purification.

For the synthesis of the other coupling partner **197** required for the annelation to give **187**, methyl acrylate and paraformaldehyde were reacted together in the presence of DABCO (Scheme 124).[106]

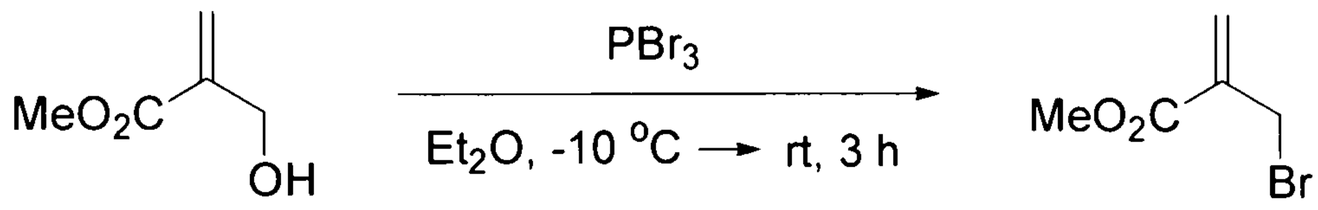


16% **199**

Scheme 124

The crude alcohol from the reaction was submitted to distillation (bp 65-70 °C/1 mm) to afford **199** as a colourless oil in only 16% yield, but comparable to that reported in the literature (lit.[107] 24%). Alternative ways to synthesise **199** in better yield exist but they were not tested.[108]

The alcohol **199** was then converted to the bromide **197** (Scheme 125).[109]

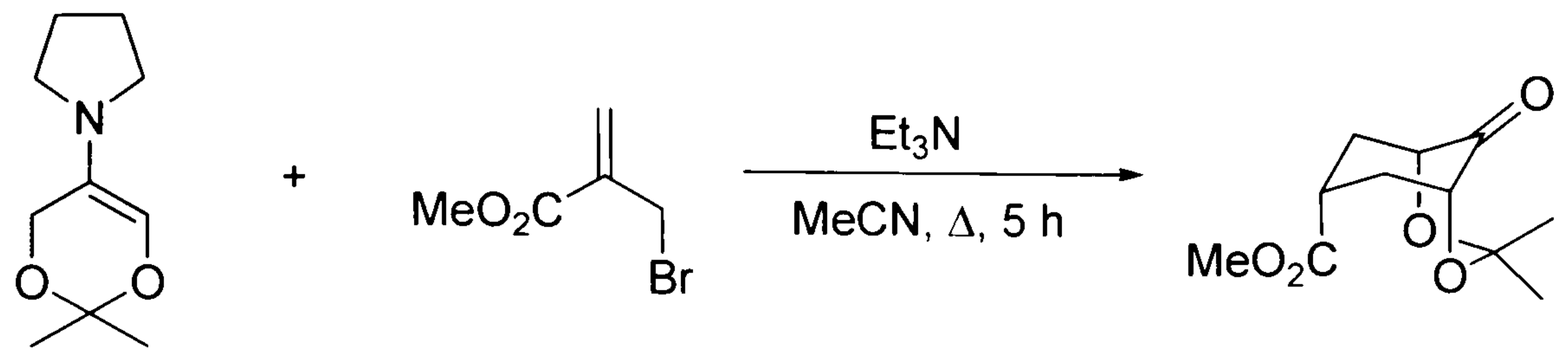


199 72% **197**

Scheme 125

Alcohol **199** was stirred with phosphorus tribromide for three hours before being subjected to a standard work-up procedure to give the bromide **197** in good yield.

Allyl bromide **197** was coupled with enamine **196** as shown in Scheme 126.

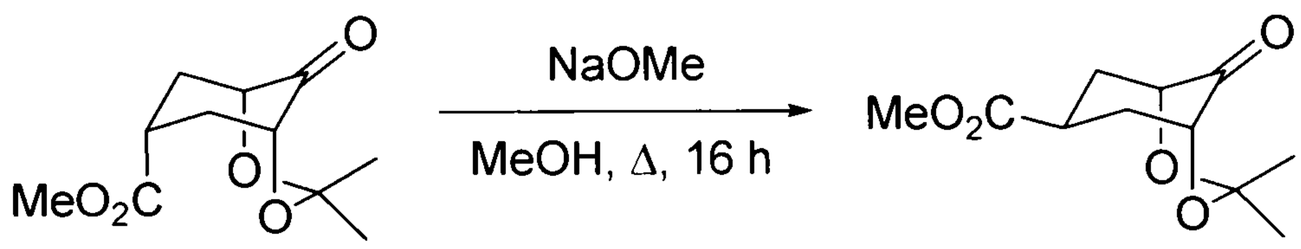


196 **197** 34% **201**

Scheme 126

The coupling partners were stirred for 5 hours under refluxing conditions in acetonitrile before being subjected to work-up. The crude product was purified by column chromatography (5:5 diethyl ether/60-80 °C petroleum ether) which afforded the bicyclic ketone **201** as a white solid in 34% yield as the main product. The novel compound was fully characterised *via* ^{1}H and ^{13}C NMR spectroscopy, low and high resolution mass-spectrometry, IR spectroscopy and melting point analysis.

The compound was then subjected to epimerisation conditions to gratifyingly afford **187** (Scheme 127).



201 47% **187**

Scheme 127

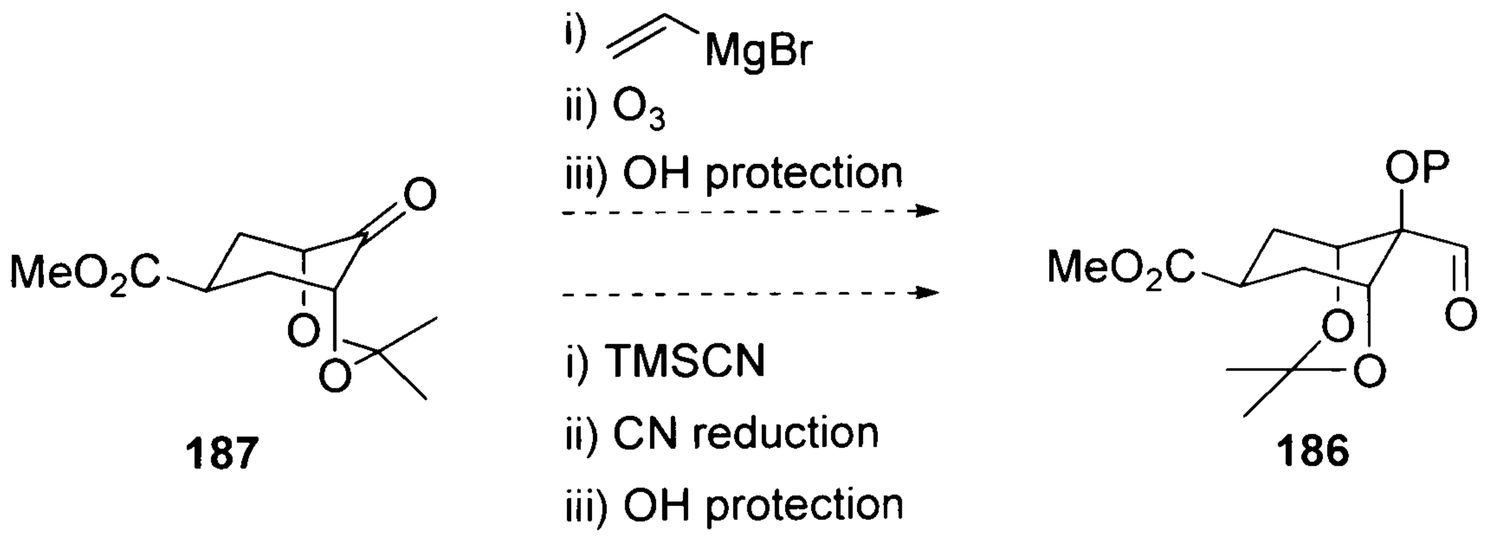
Substrate **201** was stirred under reflux in a solution of sodium methoxide in methanol overnight. The work-up afforded the novel compound **187** as a white solid which was fully characterised. Extensive ^{1}H NMR spectra analysis for compounds **201** and **187** determined the configurations of both isomers, but not their conformation. By analysis of ^{1}H NMR spectra of **201** and **187** it was possible to determine the position assumed by the methyl ester in the bicyclic ring. The high coupling costant (12.0 Hz) of the hydrogen α to the ester in **187** suggested its position as axial. Moreover its more down-shielded signal, due to anisotropic effect of the acetal functionality, compared to the same

hydrogen in **201** strongly reccomended the assignment of the configuration as shown in Scheme 127. In the ^{1}H NMR spectra the compounds are present as only one conformation, which was not possible to assign.

Section 4.4: Summary and Future work

In summation this chapter has presented work on a novel approach towards the synthesis of the methyl ester of phyllaemblic acid **183**, a natural product that has been recently isolated. The strategy could also be applied to the synthesis of similar natural products, such as **182**, **27** and **28** (Section 4.1). The key feature of this approach entails the formation of the highly oxygenated cyclohexane core **186** (Section 4.2). Herein has been reported a successful approach to establish three of the four necessary stereocentres present in the carbocyclic core of the natural product, which involved a convergent coupling reaction between substrates **196** and **197** to give **187** (Section 4.3). Acetal **187** will be employed *en route* to the future synthesis of the natural product, but its structural features will also be used to meet other synthetic targets.

It is not clear at this stage which face of the carbonyl group in **187** will be attacked, but a variety of conditions can be envisaged to ultimately favour formation of the desired axial alcohol. Two possibilities are presented below, employing either Grignard addition (kinetic control) or cyanohydrin formation (thermodynamic control).



Scheme 128

Finally, should the hydroxyl groups in **184** not be differentiated in construction of the spirocyclic acetal (Scheme 118), then they can be selectively manipulated prior to this step. In this regard, **187** and **186** are attractive substrates for asymmetric desymmetrisation, in alternative asymmetric routes to the natural products.

Chapter 5

General experimental

Melting points were recorded in open capillaries on a Büchi 510 melting point apparatus and are uncorrected.

Infrared spectra were recorded neat or as a nujol mull on a Perkin-Elmer Paragon 1600 Fourier Transform I.R. spectrometer.

NMR spectra were recorded in $CDCl_3$ at room temperature on Bruker AVANCE 360 (360 MHz ^{1}H NMR, 90 MHz ^{13}C NMR), AVANCE 400 (400 MHz ^{1}H NMR, 100 MHz ^{13}C NMR) and DRX 500 (500 MHz ^{1}H NMR, 125 MHz ^{13}C NMR) instruments using TMS ($\delta = 0$) as an internal standard, unless otherwise stated. Chemical shifts are given in parts per milion (δ ppm) and coupling constants (J) are recorded in Hertz (Hz).

Mass Spectra were obtained on a Jeol AX 505W spectrometer for low resolution EI and CI, on a Q-Tof spectrometer for low resolution ESI and on a Bruker APXIII for high resolution, on a Micromass Quattro II and Waters Micromass ZQ400 for low and high resolution FAB.

Flash Chromatography was performed using Merck silica gel (particle size 40-63 μm). Thin layer chromatography was carried out on Merck 60 F_{245} aluminum backed silica gel plates. Short wave UV light (245 nm), $KMnO_4$ or anisaldehyde were used to visualise components.

Solvents and reagents were subject to the following purification procedures:
Ethanol and *methanol* were distilled from calcium hydride.
TMEDA, *2,6-lutidine* and *acetonitrile* were distilled from calcium hydride and stored over 5 Å molecular sieves.
Toluene, *tetrachloromethane*, *dichloromethane* and *chloroform* were distilled from calcium hydride.
Diethylether was stored over sodium wire.

Purification of *m-CPBA*: *m*-CPBA (40 g) was dissolved in anhydrous diethyl ether (300 cm^3) and then washed four times with a buffer solution (410 cm^3 of 0.1 M NaOH, 250 cm^3 of 0.2 M KH_2PO_4 and 340 cm^3 of distilled water). The organic phase was dried over $MgSO_4$ and carefully evaporated *in vacuo* to give *ca.* 20 g pure *m*-CPBA.

Sodium hydride was freed of mineral oil by triturating with 60-80 °C petroleum ether.

DMSO and *DMF* were purified by distillation from calcium hydride using a high pressure vacuum pump.

Triethylamine and *diisopropylamine* were distilled from calcium hydride and stored over pellets of potassium hydroxide.

Tetrahydrofuran was distilled from sodium and benzophenone.

All other solvents and reagents were used as obtained from commercial sources.

The following cooling mixtures were obtained:

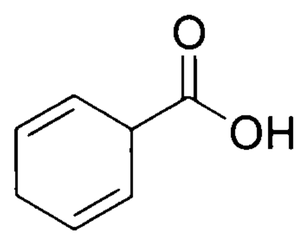
15-20 °C water/ice.

0 °C ice/water.

-5 to -78 °C acetone/cardice.

All reactions in non-aqueous solvents were carried out under argon in oven-dried glassware.

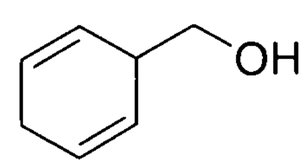
1,4-Dihydrobenzoic acid (73)[43]



73

In a 1000 cm^3 three-neck round bottomed flask fitted with an overhead stirrer, benzoic acid (10.00 g, 81.8 mmol) was dissolved in dry ethanol (100 cm^3). Liquid ammonia (600 cm^3) was condensed into the flask with the aid of a cardice/acetone condenser. Sodium (6.21 g, 270 mmol) cut in small pieces was then added to the mixture over a period of 30 minutes. Once all the sodium had dissolved, NH_4Cl (14.4 g, 270 mmol) was slowly added with stirring. The mixture was stirred for a further 1 h and then left to stand for the condensed ammonia to evaporate. The residue was dissolved in distilled water (300 cm^3) and transferred into a beaker containing 200 g of ice. The solution was then acidified to pH=4 by the addition of 1M HCl. The mixture was then extracted with diethyl ether (3×50 cm^3). The combined organic phases were then washed with saturated NaCl (100 cm^3), dried over $MgSO_4$ and finally concentrated *in vacuo* to afford the title compound **73** as a colourless oil (8.94 g, 88%), υ_{max} (neat)/cm^{-1} 2943, 2870, 1750, 1022; δ_H (360 MHz, $CDCl_3$), 2.71 (2H, m, $CHCH_2CH$), 3.77 (1H, m, $CHCOOH$), 5.78-6.00 (4H, m, 2×$CHCH$), 10.56 (1H, bs, OH); δ_C (90 MHz, $CDCl_3$) 26.2 (t), 41.9 (d), 121.9 (2×d), 127.3 (2×d), 179.5 (s); *m/z* (EI) 124 (M^+, 16%), 79 (100), 77 (50).

1,4-Dihydrobenzyl alcohol (72)[44]

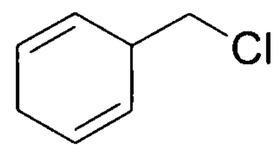


72

In a 1000 cm^3 round-bottomed flask a slurry solution of lithium aluminum hydride (5.40 g, 143.5 mmol) in diethyl ether (240 cm^3) was prepared. To this mixture a solution of 1,4-dihydrobenzoic acid **73** (8.91 g, 71.74 mmol) in diethyl ether (50 cm^3) was added slowly

such that a gentle reflux was induced. The mixture was then heated for an additional hour, cooled in an ice-bath and then hydrolysed by the cautious addition of distilled water (50 cm^3) followed by 20% wt H_2SO_4 (200 cm^3). The aqueous solution was extracted with diethyl ether (3×50 cm^3) and the combined extracts were washed with H_2O (100 cm^3), dried over $MgSO_4$ and then concentrated *in vacuo* to afford the title compound **72** as a colourless oil (7.34 g, 93%); υ_{max} (neat)/cm^{-1} 3540, 2868, 1025, 693; δ_H (360 MHz, $CDCl_3$) 2.11 (1H, s, OH), 2.68 (2H, m, CHCH_2CH), 2.93 (1H, m, CHCH_2OH), 3.61 (2H, d, *J* 4.7, CH_2OH), 5.67 (2H, m, 2×CHCH), 5.88 (2H, m, 2×CHCH); δ_C (90 MHz, $CDCl_3$) 26.8 (t), 38.8 (d), 66.6 (t), 126.1 (2×d), 127.4 (2×d); *m/z* (EI) 110 (M^+, 2.13%), 92 (24), 79 (100).

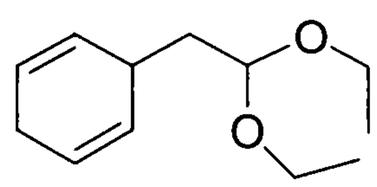
1,4-Dihydrobenzyl chloride (71)[45]



71

Triphenylphosphine (2.10 g, 8 mmol), was added to a solution of 1,4-dihydrobenzyl alcohol **72** (0.588 g, 5.3 mmol) in dry tetrachloromethane (7 cm^3) with stirring. The mixture was refluxed for 2.5 h and then allowed to cool to room temperature. It was then concentrated to a third of the volume *in vacuo*, and hexane (20 cm^3) was added to the mixture before filtering off the solid triphenylphosphine oxide precipitate. The filtrate was concentrated on a rotary evaporator and the residue was purified by distillation using a Kugelrohr apparatus (0.2 mm/Hg, 40-50 °C) to give the title compound **71** as a colourless liquid (0.233 g, 34%); υ_{max} (neat)/cm^{-1} 1302, 1022; δ_H (360 MHz, $CDCl_3$) 2.68 (2H, m, CHCH_2CH), 3.10 (1H, m, CHCH_2Cl), 3.48 (2H, d, *J* 6.1, CH_2Cl), 5.71 (2H, m, 2×CHCH), 5.87 (2H, m, 2×CHCH); δ_C (90 MHz, $CDCl_3$) 26.9 (t), 38.1 (d), 49.5 (t), 125.8 (2×d), 127.1 (2×d); *m/z* (EI) 128 (M^+; 14%), 91 (63), 79 (97), 77 (100).

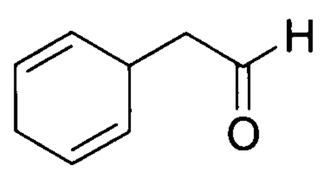
3-(2,2-Diethoxy-ethyl)-cyclohexa-1,4-diene (70)[45]



70

In a 50 cm^3 three neck round-bottomed flask, Mg (0.520 g, 22.4 mmol) was suspended in dry THF (2 cm^3) and one crystal of iodine was added. The flask was heated with a heat gun until the red solution turned colourless. A solution of 1,4-dihydrobenzyl chloride **71** (2.054 g, 15.97 mmol) in dry THF (2 cm^3) was added dropwise and the solution refluxed for 4 h. The dark coloured mixture was cooled to room temperature and diethylphenylorthoformate (3.40 cm^3, 17.57 mmol) in THF (10 cm^3) was added dropwise and the mixture was again brought to reflux. After 10 min the mixture had changed colour to light yellow. After refluxing for a further 18 h, the mixture was cooled to room temperature and an aqueous solution of 1M NH_4Cl (50 cm^3) was added. The mixture was extracted with diethyl ether (3×50 cm^3), the combined organic layers were washed with 1M HCl (3×50 cm^3), distilled water (100 cm^3), and then aqueous 1M NaOH (100 cm^3). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford the title compound **70** as a pale yellow oil (2.081 g, 66%); υ_{max} (neat)/cm^{-1} 2976, 2879, 1130, 1061; δ_H (360 MHz, $CDCl_3$) 1.21 (6H, t, *J* 7, 2×OCH_2CH_3), 1.68 (2H, t, *J* 6, CH_2CHOCH_2), 2.62 (3H, m, $CHCH_2CH$, $CHCH_2CHOCH_2$), 3.71 (4H, m, 2×OCH_2), 4.66 (1H, t, *J* 5.8, $CHCH_2CHOCH_2$), 5.68 (4H, m, 2×*CHCH*); δ_C (90 MHz, CDCl3) 15.7 (2×q), 26.5 (t), 32.3 (d), 41.1 (t), 61.4 (2×t), 101.4 (d), 124.5 (2×d), 129.2 (2×d); *m/z* (EI) 197 (M+1, 25%), 79 (96), 103 (100).

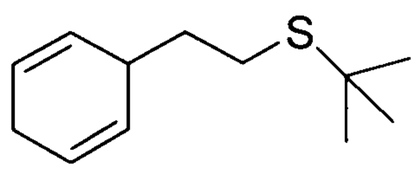
Cyclohexa-2,5-dienyl-acetaldehyde (69)[45]



69

3-(2,2-Diethoxy-ethyl)-cyclohexa-1,4-diene **70** (1.611 g, 8.22 mmol) in 10% vol H_2SO_4 (13 cm^3) was refluxed for 1 h. The reaction mixture was cooled to room temperature and extracted with diethyl ether (3×30 cm^3). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified by distillation (0.5mm/Hg, 120-140 °C) to give the title compound **69** as a colourless liquid (0.488 g, 49%); υ_{max} (neat)/cm^{-1} 2881, 2821, 1723, 1061; δ_H (360 MHz, $CDCl_3$) 2.51 (2H, dd, *J* 6.4 and 2.0, CH_2CO), 2.68 (2H, m, CHCH_2CH), 3.23 (1H, m, C*H*CH_2CO), 5.62-5.81 (4H, m, 2×C*H*C*H*), 9.76 (1H, m, COH); δ_C (90 MHz, $CDCl_3$) 25.5 (t), 30.7 (d), 50.5 (t), 125.8 (2×d), 127.7 (2×d), 202.7 (s); *m/z* (EI) 122 (M^+, 17%), 91 (93), 79 (100).

3-(2-*tert*-Butylsulfanyl-ethyl)-cyclohexa-1,4-diene (68)

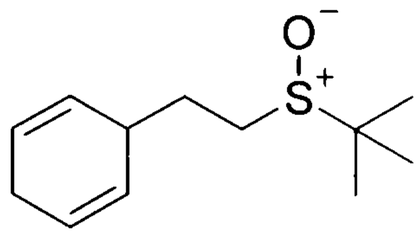


68

To a mixture of aldehyde **69** (0.456 g, 3.74 mmol) was added boron trifluoride dihydrate (0.38 cm^3, 6 mmol) and *t*-butyl thiol (0.46 cm^3, 4.1 mmol) in dichloromethane (2 cm^3) at 0 °C with stirring. After 1 min the solution had gone from colourless to pale yellow. Triethylsilane (0.72 cm^3, 4.5 mmol) was added and the mixture was allowed to warm to room temperature. After stirring for 5 h the mixture was poured on to ice-water (20 cm^3) and extracted with dichloromethane (3×25 cm^3). The combined organic layers were washed with distilled water (2×25 cm^3), saturated $NaHCO_3$ (50 cm^3), then water (50 cm^3) again and finally dried over $MgSO_4$. The mixture was filtered and then concentrated *in vacuo* to give the *title compound* **68** as a colourless liquid (0.723 g, 99%): R_f=0.3 (60-80

°C petroleum ether); υ_{max} (neat)/cm^{-1} 2959, 1364, 697; δ_H (360 MHz, $CDCl_3$) 1.32 (9H, s, 3×CH_3), 1.66-1.72 (2H, m, CH_2S), 2.51-2.56 (2H, m, CH_2CH$_2$S), 2.63-2.66 (2H, m, CHCH_2CH), 2.87-2.88 (1H, m, CHCH$_2$CH$_2$S), 5.61-5.78 (4H, m, 2×CHCH); δ_C (100 MHz, $CDCl_3$) 25.3 (t), 26.7 (t), 31.4 (3×q), 35.1 (s), 42.4 (t), 36.6 (d), 125.3 (2×d), 128.7 (2×d); *m/z* (FAB) 196 (M$^+$, 90%), 132 (100), 79 (92); HR (FAB) 197.1364 (M$^+$H $C_{12}H_{21}S$ requires 197.1360).

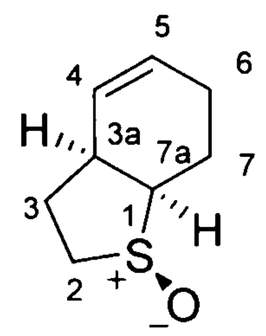
3-[2-(2-Methyl-propane-2-sulfinyl)-ethyl]-cycloexa-1,4-diene (56)



56

To a solution of 3-(2-*tert*-butylsulfanyl-ethyl)-cyclohexa-1,4-diene **68** (0.558 g, 2.8 mmol) in chloroform (1.5 cm^3), cooled in a cardice-acetone bath (-20 °C) was added a solution of *meta*-chloroperbenzoic acid (0.82 g, 3.5 mmol) in chloroform (2 cm^3). The solution was left at room temperature for 20 h then refluxed overnight. The solution was filtered and the white solid precipitate washed with saturated $NaHCO_3$ (3×10 cm^3). The aqueous layer was then extracted with dichloromethane (3×30 cm^3). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was then purified by column chromatography (2:8 diethyl ether/60-80 °C petroleum ether) to afford starting material **68** (0.065 g, 12%), the corresponding sulfone (0.042 g, 7%) and the *title compound* **56** as a colourless oil (0.244 g, 41%); R_f=0.3 (1:1 diethyl ether/60-80 °C petroleum ether); υ_{max} (neat)/cm^{-1} 2963, 1365, 1037; δ_H (360 MHz, $CDCl_3$) 1.24 (9H, s, 3×CH_3), 1.89 (1H, m, CH_2S), 2.04 (1H, m, CH_2S), 2.42-2.50 (2H, m, CH_2CH$_2$S), 2.62-2.66 (2H, m, CHCH_2CH), 3.03 (1H, m, CHCH$_2$CH$_2$S), 5.62-5.82 (4H, m, 2×CHCH); δ_C (100 MHz, $CDCl_3$) 23.3 (3×q), 26.7 (t), 29.9 (t), 34.6 (d), 42.4 (t), 53.4 (s), 126.2 (2×d), 128.1 (2×d); *m/z* (EI) 212 (M$^+$, 4%), 156 (100), 99 (79), 91 (71); HR (ESI) 235.1129 (M$^+$Na $C_{12}H_{20}OSNa$ requires 235.1127).

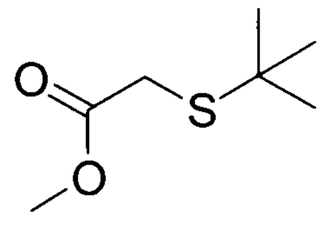
Rel (1*S*-3$_a$*S*-7$_a$*R*)-2,3,3$_a$,6,7,7$_a$-hexahydro-benzo[b]thiophene-1-oxide (58)



58

A solution of 3-[2-(2-methyl-propane-2-sulfinyl)-ethyl]-cyclohexa-1,4-diene **56** (0.075 g, 0.35 mmol) in xylene (0.14 M) was refluxed under an argon atmosphere for 3 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by column chromatography (1:9 methanol/diethyl ether) afforded the *title compound* **58** as a colourless oil (0.053 g, 97%); R_f=0.3 (1:9 methanol/diethyl ether); υ_{max} (neat)/cm^{-1} 2903, 1021; δ_H (360 MHz, DMSO) 1.58-1.65 (2H, m, 7-H), 1.95-2.00 (2H, m, 3,6-H), 2.17-2.23 (2H, m, 3,6-H), 2.50 (1H, m, 3$_a$-H), 2.69-2.72 (1H, m, 2-H), 2.81-2.88 (1H, m, 2-H), 3.42 (1H, m, 7$_a$-H), 5.74-5.84 (2H, m, 4,5-H); δ_C (100 MHz, DMSO) 18.3 (7-C), 24.1 (6-C), 31.4 (3-C), 40.1 (3$_a$-C), 52.5 (2-C), 57.4 (7$_a$-C), 128.4 (5-C), 128.5 (4-C); *m/z* (FAB) 156 (M$^+$, 100%), 135 (22); HR (FAB) 157.0680 (M$^+$H $C_8H_{13}OS$ requires 157.0687).

Methyl(2-methyl-2-propanethiol)-acetate (79)

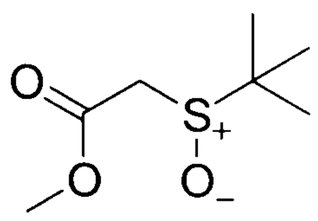


79

Pieces of sodium (1.81 g, 78.5 mmol) were dissolved in methanol (40 cm^3). The reaction was exothermic and a slow reflux started. To this solution was added, with stirring, a solution of *t*-butyl thiol (7.08 g, 78.5 mmol) in methanol (16 cm^3) and a solution of methylchloroacetate (6.9 cm^3, 78.5 mmol) in methanol (8 cm^3) at room temperature. At

this point, a white solution appeared. The resultant mixture was refluxed for 1 h. After the removal of methanol by distillation, the residue was treated with distilled water (30 cm^3), followed by extraction with diethyl ether (3×30 cm^3).The organic extract was dried over $MgSO_4$ and concentrated to dryness to afford the title compound **79** (9.87 g, 78%): analytical data agree with literature values;[110] δ_H (360 MHz, $CDCl_3$) 1.34 (9H, s, $(CH_3)_3S$), 3.31 (2H, s, CH_2S), 3.74 (3H, s, OCH_3); δ_C (90 MHz, $CDCl_3$) 31.0 (3×q), 31.5 (t), 43.4 (s), 52.8 (q), 172.0 (s).

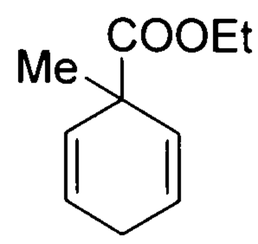
Methyl(2-methyl-2 propanesulfinyl)-acetate (78)



78

A 27% aqueous hydrogen peroxide solution (1.1 cm^3, 8.93 mmol) was added dropwise to a stirred solution of methyl(2-methyl-2-propanethiol)-acetate **79** (1.45 g, 8.93 mmol) in acetic acid (5 cm^3) at 10 °C. Stirring was continued at room temperature for 15 h and the solvent then removed *in vacuo*. The crude product was purified by column chromatography (diethyl ether) to afford the title compound **78** (1.42 g, 89%): analytical data agree with literature values:[111] δ_H (360 MHz, $CDCl_3$) 1.29 (9H, s, $(CH_3)_3S$), 3.38-3.54 (2H, d, *J* 13.6, CH_2S), 3.81 (3H, s, OCH_3); δ_c (90 MHz, $CDCl_3$) 23.1 (3×q), 51.8 (t), 53.3 (q), 54.7 (s), 176.2 (s); *m/z* (EI) 178 (M^+, 8%), 88 (95), 47 (100), 124 (51).

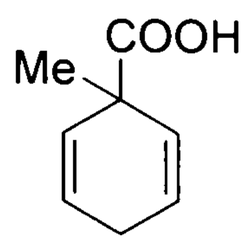
1-Methyl-cyclohexa-2,5-dienecarboxylic acid ethyl ester (86)



86

An oven dried three-necked round bottomed flask was placed under an inert atmosphere of argon. To the flask was added ethyl benzoate (8 cm^3, 55.9 mmol) dissolved in dry THF (10-15 cm^3) and *t*-BuOH (5.3 cm^3, 55.9 mmol). The reaction was cooled to -78 °C and ammonia was added (150 cm^3). Small pieces of sodium (3.2 g, 139.8 mmol) were added until the deep blue colourisation persisted for 30 min. Excess metal was quenched with piperylene (8.4 cm^3, 83.9 mmol) to give a dark orange solution. Methyl iodide (5.2 cm^3, 83.9 mmol) was then added, and the resulting solution was stirred for 1 h at -78 °C before being quenched with NH_4Cl (2 g). The reaction was allowed to warm to room temperature, and the ammonia was evaporated under an over pressure of argon. The thick mixture was diluted with distilled water (30 cm^3) and diethyl ether (30 cm^3), the phases were separated and the aqueous layer was extracted with diethyl ether (2×30 cm^3). The combined organic phases were washed with saturated $NaHCO_3$ (30 cm^3), saturated NaCl (30 cm^3), dried over $MgSO_4$ and evaporated *in vacuo* to afford the *title compound* **86** as a yellow oil (8.682 g, 93%), R_f=0.3 (diethyl ether); υ_{max} (neat)/cm^{-1} 2979, 1730, 1238, 1110; δ_H (90 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7.4, CH_2CH_3), 1.33 (3H, s, CH_3CCH), 2.65 (2H, m, $CHCH_2CH$), 4.10 (2H, q, *J* 7.1, CH_2CH_3), 5.73-5.85 (4H, m, 2×*CHCH*); δ_C (90 MHz, $CDCl_3$) 14.6 (q), 26.3 (t), 27.8 (q), 44.1 (s), 61.2 (t), 124.7 (2×d), 129.2 (2×d), 175.6 (s). *m/z* (EI) 167 (M^+H, 54%), 105 (26), 59 (17).

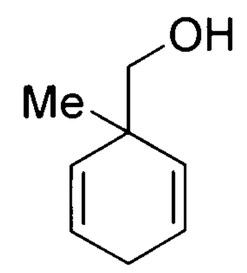
1-methyl-cyclohexa-2,5-dienecarboxylic acid (87)



87

In a 1000 cm^3 3-neck round bottom flask fitted with an overhead stirrer, benzoic acid (10 g, 81.8 mmol) was dissolved in dry THF (20 cm^3). Liquid ammonia (300 cm^3) was condensed into the flask with the aid of cardice/acetone condenser. Sodium (4.9 g, 217 mmol) was added until the blue color persisted. After the complete addition of sodium, the reaction was stirred for 15 min and then methyl iodide (7 cm^3, 114.5 mmol) was added. At this point, the reaction mixture turned pink in colour. Stirring was continued for 15 min and then NH_4Cl (11.6 g, 217 mmol) was added to quench the reaction. Evaporation of ammonia, acidification with concentrated HCl, extraction with diethyl ether (3×30 cm^3) afforded the title compound **87** as a red oil (10.77 g, 95%); analytical data agree with literature values;[112] δ_H (360 MHz, $CDCl_3$) 1.37 (3H, s, CH_3), 2.66 (2H, m, $CHCH_2CH$), 5.75-5.87 (4H, m, 2×$CHCH$), 11.01 (1H, s, OH); δ_C (90 MHz, $CDCl_3$) 26.3 (t), 27.6 (q), 44.1 (s), 125.3 (2×d), 128.5 (2×d), 182.1 (s); *m/z* (EI) 138 (M^+, 3.3%), 93 (100), 91 (80), 77 (69).

(1-methyl-cyclohexa-2,5-dienyl)-methanol (85)



85

Method A.

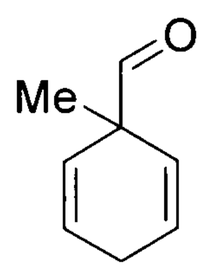
To a solution of 1-methyl-cyclohexa-2,5-dienecarboxylic acid ethyl ester **86** (7.98 g, 48 mmol) in diethyl ether (96 cm^3) at 0 °C was added lithium aluminum hydride (2.7 g, 72

mmol) in diethyl ether (72 cm^3). After 30 min at 0 °C, the reaction was quenched with distilled water (1.5 cm^3), 15% NaOH (2 cm^3) and water (2.7 cm^3) again. The mixture was filtered through Celite, dried over $MgSO_4$, and filtered. The solvent was removed *in vacuo* to afford the title compound **85** (4.75 g, 80%); analytical data agree with literature values;[51] δ_H (360 MHz, $CDCl_3$) 1.00 (3H, s, CH_3), 1.60 (1H, s, OH), 2.65 (2H, m, CHCH_2CH), 3.32 (2H, s, CH_2OH), 5.45 (2H, m, 2×C*H*CH), 5.91 (2H, m, 2×C*H*CH); δ_C (90 MHz, $CDCl_3$) 25.2 (q), 26.8 (t), 39.5 (s), 71.2 (t), 126.8 (2×d), 131.5 (2×d); *m/z* (EI) 123 (M^+; 13%), 93 (100), 77 (44).

Method B.[51]

To a slurry solution of lithium aluminum hydride (7 g, 189 mmol) in diethyl ether (90 cm^3) at 0 °C was slowly added via a dropping funnel, a solution of 1-methyl-cyclohexa-2,5-dienecarboxylic acid **87** (11.32 g, 82 mmol) in diethyl ether (250 cm^3). After the addition was complete, the reaction was allowed to stir for an additional hour. After the successive addition of distilled water, 10% NaOH and H_2O again, the white precipitate was filtered and the aqueous solution was extracted with diethyl ether (3×30 cm^3). The organic layer was dried over $MgSO_4$ and evaporated to afford the title compound **85** as a pale yellow oil (7.10 g, 70%), *data as above*.

1-Methyl-cyclohexa-2,5-diene carbaldehyde (84)

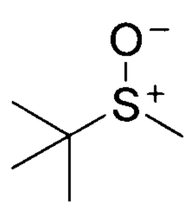


84

To a flask fitted with a low temperature thermometer was added dichloromethane (67 cm^3) and *N*-chlorosuccinimide (1.6 g, 12.2 mmol). The slighly turbid solution was cooled to 0 °C and treated with dimethyl sulfide (1.2 cm^3, 16.3 mmol) which resulted in the formation of a flocculent white precipitate. The mixture was cooled to -25 °C and a solution of (1-methyl-cyclohexa-2,5-dienyl)-methanol **85** (1.000 g, 8.13 mmol) in

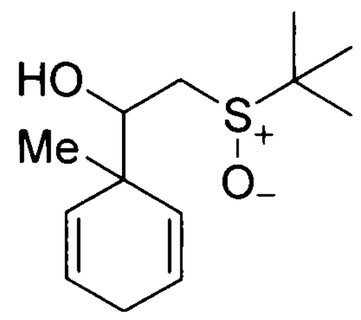
dichloromethane (6 cm^3) was slowly added to maintain the temperature below -22 °C. The mixture was stirred at -25 °C for an additional 2 h and then triethylamine (2 cm^3, 14.3 mmol) was added. The mixture was poured into distilled water (20 cm^3) and extracted with dichloromethane (3×20 cm^3) to afford the crude aldehyde (1.448 g, 147%). Purification of the aldehyde by distillation using Kugelrohr apparatus (0.4 mmHg, 20-40 °C) gave the title compound **84** as a colourless oil (0.517 g, 53 %); analytical data agree with literature values;[113] υ_{max} (neat)/cm^{-1} 2873, 2800, 1718, 1050; δ_C (360 MHz, $CDCl_3$) 1.23 (3H, s, CH_3), 2.74 (2H, m, CHCH_2CH), 5.45 (2H, m, 2×C*H*CH), 5.98 (2H, m, 2×C*H*CH), 9.33 (1H, s, CO*H*); δ_C (90 MHz, $CDCl_3$) 21.9 (q), 26.8 (t), 50.6 (s), 126.4 (2×d), 127.8 (2×d), 199.7 (d); *m/z* (EI) 121 (M^+;13), 107 (100), 105 (50).

t-Butyl methyl sulfoxide (75)



Powdered sodium periodate (10.3 g, 48 mmol) was placed in a round bottomed flask with a magnetic stirrer. A solution of distilled water and methanol (105 cm^3) in a ratio of 90:15 was added over a period of 10 minutes. The mixture was stirred whilst cooling in an ice-bath. *t*-Butyl methyl sulfide (5 g, 48 mmol) was added and the mixture was stirred for 20 h. The mixture was then filtered, and the filter cake of sodium iodate was washed with dichloromethane (3×20 cm^3). The organic filtrate was transferred to a separating funnel and the aqueous layer extracted with dichloromethane (3×25 cm^3). The combined dichloromethane extract was dried over $MgSO_4$ and the solvent removed under reduced pressure to afford the title compound **75** as a pale yellow oil (5.566 g, 97%); analytical data agree with literature values;[114] δ_H (360 MHz, $CDCl_3$) 1.25 (9H, s, 3×CH_3), 2.38 (3H, s, CH_3); δ_C (90 MHz, $CDCl_3$) 22.8 (3×q), 31.9 (q), 52.8 (s).

Rel-(1*R*)-1-(1-methyl-cyclohexa-2,5-dienyl)-2-((*S*)-*t*-butylsulfinyl)-ethanol (83a) and rel-(1*R*)-1-(1-methyl-cyclohexa-2,5-dienyl)-2-((*R*)-*t*-butylsulfinyl)-ethanol (83b)



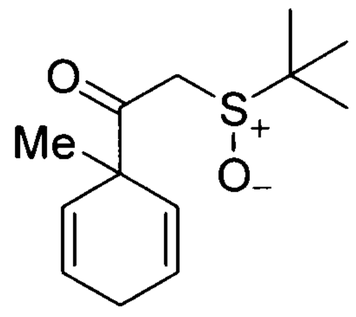
To a solution of lithium diisopropylamide (6.3 mmol) in dry THF (6 cm^3) at -78 °C was added dropwise a solution of *t*-butyl methyl sulfoxide **75** (0.6 g, 5.1 mmol) in THF (5 cm^3). The mixture was stirred for 2 h. 1-Methyl-cyclohexa-2,5-diene carbaldehyde **84** (0.93 g, 7.6 mmol) was then added and the mixture was stirred at -78 °C for 3 h. The solution was warmed to room temperature, quenched with saturated NH_4Cl (30 cm^3) and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3×20 cm^3) and the combined organic extracts were washed with saturated NaCl (30 cm^3) and dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (diethyl ether) to afford the *title compound* **83a** (0.36 g, 29%) as a white solid, followed by the *title compound* **83b** (0.40 g, 33%) as a white solid: **83a** R_f=0.4 (diethyl ether); mp 42 °C; υ_{max} (neat)/cm^{-1} 3440, 1633, 1450, 1060; δ_H (360 MHz, $CDCl_3$) 1.22 (3H, s, CH_3CCH), 1.23 (9H, s, (CH_3)$_3$CS), 2.47-2.55 (2H, m, CH_2S), 2.56-2.66 (2H, m, CHCH_2CH), 4.02 (1H, m, C*H*OH), 4.43 (1H, s, OH), 5.43-5.47 (1H, m, C*H*CH), 5.73-5.85 (3H, m, 3×C*H*CH); δ_C (90 MHz, $CDCl_3$) 23.0 (3×q), 26.1 (q), 27.2 (t), 41.8 (s), 45.7 (t), 54.2 (s), 75.8 (d), 125.1 (d), 125.8 (d), 129.7 (d), 131.9 (d); *m/z* (EI) 243 (M^+H, 21%), 149 (30), 93 (100), 57 (66); HR (ESI) 265.1232 (M^+Na $C_{13}H_{22}O_2SNa$ requires 265.1233); **83b** R_f=0.1 (diethyl ether); mp 147 °C; υ_{max} (neat)/cm^{-1} 3421, 1643, 1462, 1022; δ_H (360 MHz, $CDCl_3$) 1.18 (3H, s, CH_3CCH), 1.24 (9H, s, (CH_3)$_3$CS), 2.46-2.66 (4H, m, CHCH_2CH, CH_2S), 3.01 (1H, d, *J* 4.2, OH), 3.95-4.00 (1H, m, C*H*OH), 5.43-5.47 (1H, m, C*H*CH), 5.66-5.70 (1H, m, C*H*CH), 5.80-5.89 (2H, m, 2×C*H*CH); δ_C (90 MHz, $CDCl_3$) 22.6 (3×q), 25.4 (q), 26.3 (t), 40.8 (s), 48.4 (t), 52.4 (s), 71.9 (d), 125.2

(d), 125.3 (d), 129.1 (d), 130.2 (d); *m/z* (EI) 243 (M^+H, 55%), 149 (93), 94 (100), 77 (64): HR (ESI) 243.1403 (M^+H $C_{13}H_{23}O_2S$ requires 243.1419).

Method B: **83b** from **88**.

To a solution of 1-(1-methyl-cyclohexa-2,5-dienyl)-2-(*t*-butylsulfinyl)-ethanone **88** (0.250 g, 1 mmol) in dry THF (10 cm^3) at –78 °C was added dropwise a 1M solution of diisobutylaluminum hydride in toluene (1.1 cm^3, 1.1 mmol). After 1 h at –78 °C, methanol (10 cm^3) was added to the reaction vessel. The solvent was then evaporated *in vacuo* and the residue diluted with distilled water (10 cm^3) and extracted with dichoromethane (3×20 cm^3). The organic layer was then washed with a 5% NaOH solution (20 cm^3), dried over $MgSO_4$ and evaporated *in vacuo* to afford the title compound **83b** as a white solid (0.231 g, 96%), R_f=0.1 (diethyl ether), *data as above*.

1-(1-Methyl-cyclohexa-2,5-dienyl)-2-(*t*-butylsulfinyl)-ethanone (88)

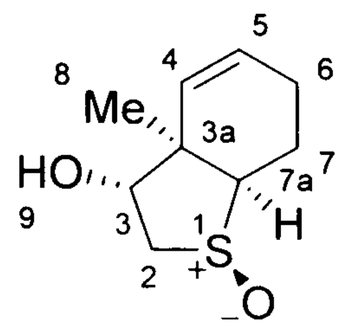


88

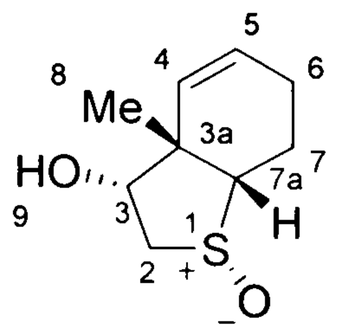
To a solution of lithium diisopropylamide (9.7 mmol) in dry THF (9 cm^3) at -78 °C was added dropwise a solution of *t*-butyl methyl sulfoxide **75** (1.004 g, 8.4 mmol) in THF (2 cm^3). The reaction was stirred for 2 h. 1-Methyl-cyclohexa-2,5-dienecarboxylic acid ethyl ester **86** (0.700 g, 4.2 mmol) was then added and the reaction was stirred at -78 °C for a further 3 h. The reaction was then allowed to warm to room temperature, quenched with saturated NH_4Cl (20 cm^3) and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3×20 cm^3) and the combined organic extracts were washed with saturated NaCl (30 cm^3), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (diethyl ether) to afford the *title compound* **88** as a pale yellow oil (0.772 g, 76%), R_f=0.3 (diethyl ether); υ_{max} (neat)/cm^{-1}

2928, 1710, 1367, 1048; δ_H (360 MHz, $CDCl_3$) 1.24 (9H, s, $(CH_3)_3CS$), 1.30 (3H, s, CH_3CCH), 2.78-2.83 (2H, m, $CHCH_2CH$), 3.68 (2H, d, *J* 8.5, CH_2S), 5.50-5.57 (2H, m, 2×C*H*CH), 5.95-6.02 (2H, m, 2×C*H*CH); δ_C (90 MHz, $CDCl_3$) 23.2 (3×q), 24.0 (q), 26.5 (t), 52.6 (s), 54.5 (s), 55.6 (t), 127.2 (d), 127.4 (d), 128.4 (d), 128.6 (d), 203.6 (s); *m z* (FAB) 241 (M^+H, 42%), 167 (40), 154 (100), 136 (87); HR (FAB) 241.3543 (M^+H $C_{13}H_{21}O_2S$ requires 241.3527).

Rel-(1*S*,3*R*,3$_a$*R*,7$_a$*R*)-3$_a$-methyl-1-oxo-2,3,3$_a$,6,7,7$_a$-hexahydro-1*H*-1λ^4-benzo[*b*]thiophen-3-ol (91a) and *rel*-(1*R*,3*R*,3$_a$*S*,7$_a$*S*)-3$_a$-methyl-1-oxo-2,3,3$_a$,6,7,7$_a$-hexahydro-1*H*-1λ^4-benzo[*b*]thiophen-3-ol (91b)



91a



91b

A solution of *rel*-(1*R*)-1-(1-methyl-cyclohexa-2,5-dienyl)-2-((*R*)-*t*-butylsulfinyl)-ethanol **83b** (1.78 g, 7.4 mmol) was placed under an inert atmosphere of argon and refluxed in xylene (0.14 M) for 3.5 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by column chromatography (4:96 methanol/diethyl ether) afforded the starting material **83b** (0.25 g, 14%) followed by the *title compounds* **91a** as a white solid (0.28 g, 20%) and **91b** as a white solid (0.29 g, 21%); **91a** R_f=0.3 (4:96 methanol/diethyl ether); mp 140 °C; υ_{max} (neat)/cm^{-1} 3282, 2980, 1027, 999; δ_H (500 MHz, $CDCl_3$) 1.16 (3H, s, 8-H), 1.94-2.02 (2H, m, 6,7-H), 2.19-2.26 (1H, m, 7-H), 2.45-2.49 (1H, m, 6-H), 2.87-2.92 (1H, dd, *J* 12.7 and 4.0, 2-H), 3.20 (1H, t, *J* 4.7, 7$_a$-H), 3.61 (1H, dd, *J* 12.7 and 3.2, 2-H), 3.67 (1H, s, 9-H), 4.26 (1H, d, *J* 2.9, 3-H), 5.52 (1H, d, *J* 10.9, 4-H), 5.84-5.89 (1H, m, 5-H); δ_C (125 MHz, $CDCl_3$) 18.1 (7-C), 22.8 (8-C), 23.2 (6-C), 47.7 (3$_a$-C), 59.2 (7$_a$-C), 59.8 (2-C), 78.8 (3-C), 129.2 (5-C), 130.6 (4-C); *m z* (FAB) 187 (M^+H, 100%), 132 (67), 93 (13); HR (FAB) 186.0800 (M^+ $C_9H_{14}O_2S$ requires 186.0793); **91b** R_f=0.2

(4:96 methanol/diethyl ether); mp 125 °C; υ_{max} (neat)/cm^{-1} 3190, 2948, 1033, 908; δ_H (500 MHz, $CDCl_3$) 1.08 (3H, s, 8-H), 1.98-2.25 (3H, m, 6,7-H), 2.42 (1H, m, 6-H), 3.03 (1H, dd, *J* 9.0 and 5.8, 7_a-H), 3.15-3.25 (2H, m, 2-H), 3.47 (1H, d, *J* 7.5, 9-H), 4.18-4.22 (1H, m, 3-H), 5.77-5.80 (1H, m, 4-H), 6.05-6.10 (1H, m, 5-H); δ_C (125 MHz, $CDCl_3$) 20.3 (7-C), 23.5 (6-C), 28.4 (8-C), 49.2 (3_a-C), 56.3 (2-C), 65.5 (7_a-C), 83.0 (3-C), 129.8 (5-C), 130.1 (4-C); *m/z* (EI) 187 (M^+H, 100%), 119 (18), 95 (55); HR (FAB) 186.0800 (M^+ $C_9H_{14}O_2S$ requires 186.0793).

Method B: from **83a**.

A solution of *rel*-(1*R*)-1-(1-methyl-cyclohexa-2,5-dienyl)-2-((*S*)-*t*-butylsulfinyl)-ethanol **83a** (0.079 g, 0.33 mmol) was placed under an inert atmosphere of argon and refluxed in xylene (0.14 M) for 3 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by column chromatography (1% methanol in diethyl ether) afforded the title compound **91a** (0.18 g, 29%) and **91b** (0.17 g, 28%), *data as above*.

Method C: **91a** from **94a**.

A solution of *rel*-(1*S*,3*R*,3_a*R*,7_a*R*)-acetic acid 3_a-methyl-1-oxo-2,3,3_a,6,7,7_a-hexahydro-1*H*-1λ^4-benzo[*b*]thiophen-3-yl ester **94a** (0.116 g, 0.51 mmol) in methanol (5 cm^3) was added to a solution of NaOH (0.14 g, 3.56 mmol) in methanol (10 cm^3) at room temperature. After 0.5 h, methanol was removed *in vacuo* and distilled water (6 cm^3) was added. The resulting solution was extracted with (50:50) benzene-ethyl acetate (3×20 cm^3). The organic extract was washed with water (30 cm^3), filtered and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford the title compound **91a** (0.062 g, 38%), *data as above*.

Method D: **91a** from **97a**.

Tetrabutylammonium fluoride (0.8 cm^3, 0.8 mmol) was added dropwise to a stirred solution of *rel*-(1*S*,3*R*,3_a*R*,7_a*R*)-3-(*tert*-butyl-dimethylsilyl)oxy-3_a-methyl-2,3,3_a,6,7,7_a-hexahydro-benzo[*b*]thiophene1-oxide **97a** (0.048 g, 0.16 mmol) in THF (1 cm^3) at 0 °C. After 4 h, the reaction mixture was subjected to an extractive work-up (NH_4Cl/NH_4OH

pH=8 buffer/diethyl ether). The resulting organic layer was then dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford the title compound **91a** (0.009 g, 30%), *data as above*.

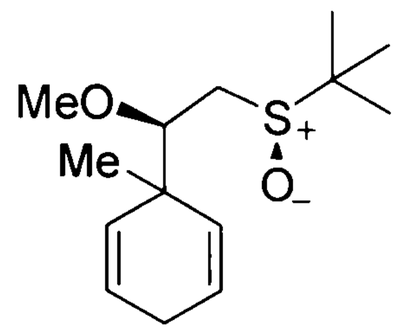
Method C: **91b** from **94b**.

A solution of *rel*-(1*R*,3*R*,3$_a$*S*,7$_a$*S*)-acetic acid 3a-methyl-1-oxo-2,3,3$_a$,6,7,7$_a$-hexahydro-1*H*-1λ^4-benzo[b]thiophen-3-yl ester **94b** (0.048 g, 0.21 mmol) in methanol (1 cm^3) was added to a solution of NaOH (0.059 g, 1.47 mmol) in methanol (6 cm^3) at room temperature. After 0.5 h, methanol was removed *in vacuo* and distilled water (3 cm^3) was added. The resulting solution was extracted with (50:50) benzene-ethyl acetate (3×10 cm^3). The organic extract was washed with water (15 cm^3), filtered and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford the title compound **91b** (0.016 g, 41%), *data as above*.

Method D: **91b** from **95b**.

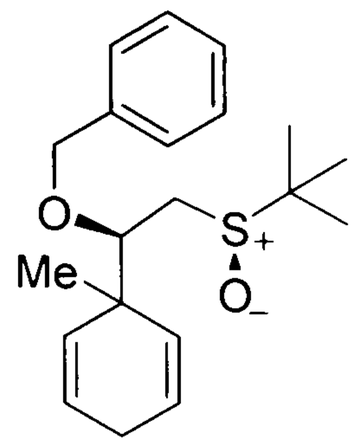
A solution of *rel*-(1*R*,3*R*,3$_a$*S*,7$_a$*S*)-benzoic acid 3$_a$-methyl-1-oxo-2,3,3$_a$,6,7,7$_a$-hexahydro-1*H*-1λ^4-benzo[*b*]thiophen-3-yl ester **95b** (0.028 g, 0.097 mmol) in methanol (3.5 cm^3) was added to a solution of NaOH (0.027 g, 0.68 mmol) in methanol (8 cm^3) at room temperature. After 0.5 h, methanol was removed *in vacuo* and distilled water (6 cm^3) was added. The resulting solution was extracted with (50:50) benzene-ethyl acetate (3×20 cm^3). The organic extract was washed with water (30 cm^3), filtered and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford the title compound **91b** (0.006 g, 33%), *data as above*.

Rel-(1_R_)-1-(1-methyl-cyclohexa-2,5-dienyl)-1-methoxy-2-((_R_)-_t_-butylsulfinyl)-ethane (92)



To a stirred suspension of sodium hydride (0.50 mmol) in dry THF (1 cm^3) at 0 °C was added dropwise a solution of *rel*-(1*R*)-1-(1-methyl-cyclohexa-2,5-dienyl)-2-((*R*)-*t*-butylsulfinyl)-ethanol **83b** (0.086 g, 0.36 mmol) in THF (2 cm^3). Methyl iodide (0.02 cm^3, 0.36 mmol) was added after 2 h at 0 °C. The reaction was allowed to warm to room temperature overnight. The reaction was then quenched with distilled water (20 cm^3) and the aqueous layer was extracted with diethyl ether (3×20 cm^3). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by column chromatography (7:3 diethyl ether/60-80 °C petroleum ether) to afford the *title compound* **92** as a colourless oil (0.061 g, 66%), R_f=0.3 (7:3 diethyl ether/60-80 °C petroleum ether); υ_{max} (neat)/cm^{-1} 2928, 1103, 1025; δ_H (360 MHz, $CDCl_3$) 1.19 (3H, s, CH_3CCH), 1.21 (9H, s, (CH_3)$_3$CS), 2.41-2.70 (4H, m, CHCH_2CH, CH_2S), 3.52 (1H, dd, *J* 10.7 and 1.8, C*H*OCH$_3$), 3.64 (3H, s, CH_3O), 5.45-5.82 (4H, m, 2×C*H*C*H*); δ_C (90 MHz, $CDCl_3$) 23.2 (3×q), 26.5 (q), 27.0 (t), 42.3 (s), 50.4 (t), 53.0 (s), 62.3 (d), 82.6 (q), 125.2 (d), 125.3 (d), 129.9 (d), 131.9 (d); *m/z* (FAB) 257 (M^+H, 95%), 169 (100), 136 (42), 119 (56); HR (FAB) 257.1586 (M^+H $C_{14}H_{25}O_2S$ requires 257.1575).

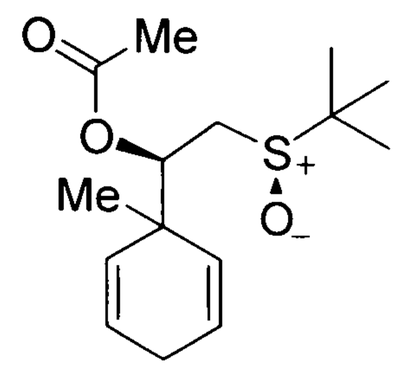
Rel-(1_R_)-1-(1-methyl-cyclohexa-2,5-dienyl)-1-benzyloxy-2-((_R_)-_t_-butylsulfinyl)-ethane (93)



93

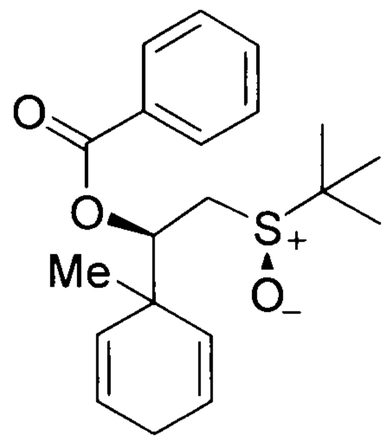
To a stirred suspension of sodium hydride (0.91 mmol) in dry THF (5 cm^3) at 0 °C was added dropwise a solution of *rel*-(1*R*)-1-(1-methyl-cyclohexa-2,5-dienyl)-2-((*R*)-*t*-butylsulfinyl)-ethanol **83b** (0.157 g, 0.65 mmol) in THF (2 cm^3). Benzyl bromide (0.07 cm^3, 0.65 mmol) was added after 2 h at 0 °C. The reaction was then allowed to warm to room temperature overnight. The reaction was quenched with distilled water (30 cm^3) and the aqueous layers extracted with diethyl ether (3×25 cm^3). The combined organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by column chromatography (9:1 diethyl ether/60-80 °C petroleum ether) to afford the *title compound* **93** as a white solid (0.160 g, 74%), R_f=0.2 (9:1 diethyl ether/60-80 °C ether petroleum); mp 160 °C; υ_{max} (neat)/cm^{-1} 3029, 1633, 1456, 1071, 1042; δ_H (360 MHz, $CDCl_3$) 1.22 (9H, s, $(CH_3)_3CS$), 1.24 (3H, s, CH_3CCH), 2.52-2.74 (4H, m, $CHCH_2CH$, CH_2S), 3.82 (1H, dd, *J* 10.5 and 1.7, $CHOCH_2$), 4.73 (1H, d, *J* 10.8, $CHOCH_2$), 4.96 (1H, d, *J* 10.8, $CHOCH_2$), 5.51-5.82 (4H, m, 2×$CHCH$), 7.26-7.50 (5H, m, 5×Ar-*H*); δ_C (90 MHz, $CDCl_3$) 23.3 (3×q), 27.0 (t), 27.1 (q), 42.4 (s), 50.5 (t), 53.1 (s), 76.0 (t), 80.7 (d), 125.3 (d), 128.0 (d), 128.0 (d), 128.3 (d), 128.7 (d), 129.3 (d), 129.9 (d), 130.2 (d), 132.0 (d), 138.8 (s); *m/z* (EI) 333 (M^+H, 3%), 183 (79), 152 (53), 91 (100); HR (ESI) 333.1900 (M^+H $C_{20}H_{29}O_2S$ requires 333.1888).

Rel-(1_R_)-acetic acid 1-(1-methyl-cyclohexa-2,5-dienyl)-2-((_R_)-_t_-butylsulfinyl)-ethyl ester (94)



Rel-(1*R*)-1-(1-methyl-cyclohexa-2,5-dienyl)-2-((*R*)-*t*-butylsulfinyl)-ethanol **83b** (0.111 g, 0.46 mmol) was stirred with acetic anhydride (0.44 cm^3, 4.6 mmol) and a catalytic amount of 4-dimethylaminopyridine (0.006 g, 0.05 mmol) at 65 °C for 2 h. The reaction was allowed to cool to room temperature and was poured into distilled water (3 cm^3). The solution was neutralised with saturated $NaHCO_3$ (20 cm^3) and extracted with dichloromethane (3×20 cm^3). The organic layers were collected, dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was then purified by column chromatography (diethyl ether) to give the *title compound* **94** as a colourless oil (0.100 g, 77%). R_f=0.2 (diethyl ether); υ_{max} (neat)/cm^{-1} 2966, 1748, 1236, 1042; δ_H (360 MHz, $CDCl_3$) 1.02 (3H, s, CH_3CCH), 1.13 (9H, s, (CH_3)$_3$CS), 2.04 (3H, s, CH_3CO), 2.49-2.55 (4H, m, CHCH_2CH, CH_2S), 5.28 (1H, dd, *J* 7.4 and 5.1, C*H*OCO), 5.40-6.14 (4H, m, 2×C*H*C*H*); δ_C (100 MHz, $CDCl_3$) 21.2 (q), 23.1 (3×q), 26.3 (q), 26.8 (t), 41.0 (s), 49.5 (t), 53.2 (s), 73.4 (d), 125.8 (d), 126.0 (d), 128.9 (d), 130.4 (d), 170.2 (s); *m/z* (EI) 285 (M^+H, 6%), 119 (33), 105 (100), 57 (79); HR (ESI) 307.1341 (M^+Na $C_{15}H_{24}SO_3Na$ requires 307.1338).

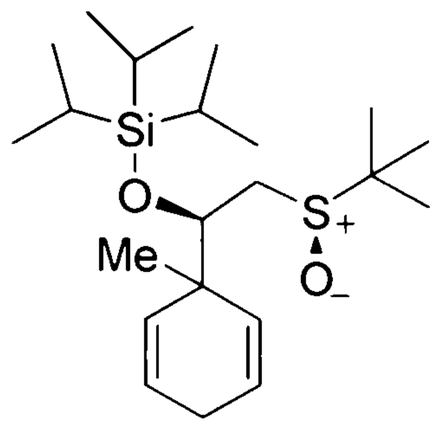
Rel-(1_R_)-benzoic acid 1-(1-methyl-cyclohexa-2,5-dienyl)-2-((_R_)-_t_-butylsulfinyl)-ethyl ester (95)



95

To a solution of *rel*-(1*R*)-1-(1-methyl-cyclohexa-2,5-dienyl)-2-((*R*)-*t*-butylsulfinyl)-ethanol **83b** (0.230 g, 0.95 mmol) in dry THF (10 cm^3) at –78 °C was added *n*-butyllithium (0.45 cm^3, 0.95 mmol). After stirring for 0.5 h, the solution was transferred dropwise to a solution of benzoyl chloride (0.22 cm^3, 1.9 mmol) in THF (10 cm^3). After stirring for 4.5 h, a solution of 10% Na_2CO_3 (10 cm^3) was added and the resulting two-phase mixture was stirred at 20 °C for 1 h. The THF was then evaporated, and the resulting aqueous solution was diluted with distilled water (20 cm^3) and extracted with diethyl ether (3×30 cm^3). The combined organic layers were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude compound was purified by column chromatography (diethyl ether) to afford the *title compound* **95** as a white solid (0.176 g, 54%), R_f=0.2 (diethyl ether); mp 160 °C; υ_{max} (neat)/cm^{-1} 1716, 1273, 1112; δ_H (360 MHz, $CDCl_3$) 1.14 (3H, s, C*H*$_3$CCH), 1.21 (9H, s, (C*H*$_3$)$_3$CS), 2.65-2.70 (2H, m, C*H*$_2$S), 2.73-2.81 (2H, m, CHC*H*$_2$CH), 5.57-5.60 (1H, m, C*H*CH), 5.64 (1H, dd, *J* 3.1 and 6.2, C*H*OCO), 5.74-5.77 (1H, m, C*H*CH), 5.87-5.91 (2H, m, 2×C*H*CH), 7.44-7.48 (2H, m, 2×Ar-*H*), 7.56-7.60 (1H, m, 1×Ar-*H*), 8.07 (2H, m, 2×Ar-*H*); δ_C (90 MHz, $CDCl_3$), 23.0 (q), 27.0 (t), 31.2 (s), 31.3 (3×q), 47.1 (s), 58.0 (t), 80.8 (d), 126.4 (d), 128.8 (d), 129.0 (d), 129.1 (d), 130.0 (d), 130.2 (d), 130.6 (d), 133.5 (s), 134.0 (d); *m/z* (EI) 347 (M^+H, 75%), 291 (45), 243 (12), 176 (16); HR (ESI) 347.5424 (M^+H $C_{20}H_{27}O_3S$ requires 347.5410).

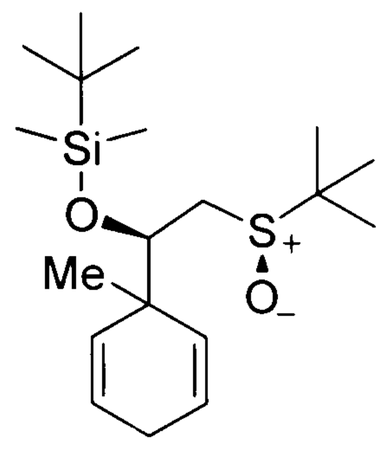
Rel-(1_R_)-1-(1-methyl-cyclohexa-2,5-dienyl)-1-(tri-isopropylsilyl)oxy-2-((_R_)-_t_-butylsulfinyl)-ethane (96)



96

To a stirred solution of *rel*-(1*R*)-1-(1-methyl-cyclohexa-2,5-dienyl)-2-((*R*)-*t*-butylsulfinyl)-ethanol **83b** (0.209 g, 0.87 mmol) in dichloromethane (1.5 cm^3) was added 2,6-lutidine (0.15 cm^3, 1.31 mmol) and triisopropylsilyl trifluoromethanesulfonate (0.28 cm^3, 1 mmol) at -78 °C. The solution was allowed to warm to room temperature and stirred overnight. Then saturated $NaHCO_3$ (3 cm^3) was added and the reaction mixture was poured into dichloromethane (5-10 cm^3) and diluted with distilled water (5 cm^3). The layers were separated and the aqueous phase was extracted with dichloromethane (3×10 cm^3). The combined organic layer was dried over $MgSO_4$, filtered and the solvent evaporated *in vacuo*. The crude compound was purified by column chromatography (4:6 diethyl ether/60-80 °C petroleum ether) to afford the *title compound* **96** as a colourless oil (0.194 g, 56%), R_f=0.28 (2:3 diethyl ether/60-80 °C petroleum ether); υ_{max} (neat)/cm^{-1} 1104, 1047; δ_H (360 MHz, $CDCl_3$) 1.12 (21H, m, C*H*Si, CH_3CHSi), 1.15 (3H, s, CH_3CCH), 1.2 (9H, s, (CH_3)$_3$CS), 2.19 (1H, dd, *J* 13.1 and 9.3, CH_2S), 2.61-2.64 (2H, m, CHCH_2CH), 2.76 (1H, dd, *J* 13.1 and *J* 0.9, CH_2S), 4.17 (1H, d, *J* 8.7, C*H*OSi), 5.46-5.50 (1H, m, C*HCH*), 5.74-5.82 (3H, m, 2×C*HCH*); δ_C (90 MHz, $CDCl_3$) 14.1 (6×q), 18.9 (3×d), 19.1 (q), 23.4 (3×q), 27.2 (t), 43.0 (s), 52.6 (t), 53.2 (s), 74.0 (d), 124.9 (d), 125.1 (d), 129.9 (d), 132.9 (d); *m/z* (EI) 399 (M^+H, 3%), 355 (100), 249 (74), 193 (70), 157(58); HR (ESI) 399.2757 (M^+H $C_{22}H_{43}O_2SSi$ requires 399.2748).

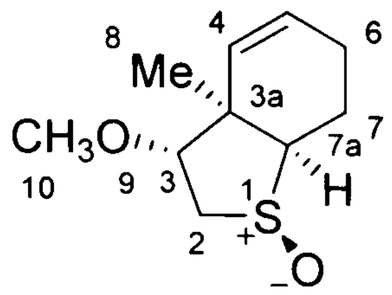
Rel-(1_R_)-1-(1-methyl-cyclohexa-2,5-dienyl)-1-(_t_-butyl-dimethylsilyl)oxy-2-((_R_)-_t_-butylsulfinyl)-ethane (97)



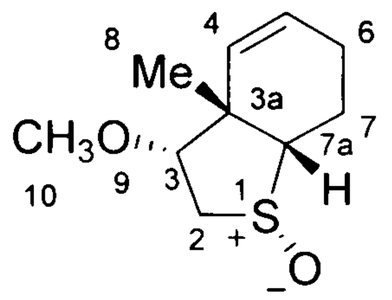
97

To a stirred solution of *rel*-(1*R*)-1-(1-methyl-cyclohexa-2,5-dienyl)-2-((*R*)-*t*-butylsulfinyl)-ethanol **83b** (0.289 g, 1.2 mmol) and imidazole (0.2 g, 3 mmol) in anhydrous *N*,*N*-dimethylformamide (0.6 cm^3) was added a solution of *t*-butyldimethylsilyl chloride (0.43 g, 2.9 mmol) in *N*,*N*-dimethylformamide (0.5 cm^3). The solution was stirred for 2 d at room temperature under an inert atmosphere of argon. Then distilled water (30 cm^3) was added and the aqueous layer was extracted with dichloromethane (3×25 cm^3). The combined organic layer was dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude compound was purified by column chromatography (5:5 diethyl ether/60-80 °C petroleum ether) to give the starting material **83b** (0.142 g, 49%) and the *title compound* **97** as a colourless oil (0.200 g, 47%), R_f=0.3 (1:1 diethyl ether/60-80 °C petroleum ether); υ_{max} (neat)/cm^{-1} 2929, 1077, 1041; δ_H (360 MHz, $CDCl_3$) 0.14 (3H, s, $(CH_3)_2Si$), 0.18 (3H, s, $(CH_3)_2Si$), 0.92 (9H, s, $(CH_3)_3CSi$), 1.15 (3H, s, CH_3CCH), 1.19 (9H, s, $(CH_3)_3CS$), 2.33 (1H, dd, *J* 13.3 and 1.9, CH_2S), 2.49-2.71 (2H, m, $CHCH_2CH$), 2.94 (1H, dd, *J* 13.3 and 8.3, CH_2S), 4.02 (1H, dd, *J* 8.2 and 1.9, *CH*OSi), 5.57-5.86 (4H, m, 2×*CHCH*); δ_C (90 MHz, $CDCl_3$) 0.0 (2×q), 18.4 (s), 23.1 (3×q), 26.4 (3×q), 27.2 (t), 27.5 (q), 42.8 (s), 52.9 (t), 53.3 (s), 73.9 (d), 125.1 (d), 125.4 (d), 129.8 (d), 132.3 (d); *m/z* (EI) 357 (M^+H, 13%), 207 (91), 169 (80), 119 (100); HR (ESI) 357.2270 (M^+H $C_{19}H_{37}O_2SSi$ requires 357.2284).

***Rel*-(1*S*,3*R*,3$_a$*R*,7$_a$*R*)-3-methoxy-3$_a$-methyl-2,3,3$_a$,6,7,7$_a$-hexahydro-benzo[*b*]thiophene-1-oxide (92a) and *rel*-(1*R*,3*R*,3$_a$*S*,7$_a$*S*)-3-methoxy-3$_a$-methyl-2,3,3$_a$,6,7,7$_a$-hexahydro-benzo[*b*]thiophene-1-oxide (92b)**



92a



92b

A solution of *rel*-(1*R*)-1-(1-methyl-cyclohexa-2,5-dienyl)-1-methoxy-2-((*R*)-*t*-butylsulfinyl)-ethane **92** (0.11 g, 0.43 mmol) was placed under an inert atmosphere of argon and refluxed in xylene (0.14 M) for 3 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by column chromatography (diethyl ether) afforded a mixture of cycloadducts **92a** and **92b** (0.06 g, 65%, dr 4:1), R_f=1.5 (diethyl ether); **92a** (major diastereoisomer), colourless oil, υ_{max} (neat)/cm^{-1} 2938, 1043, 1002; δ_H (500 MHz, $CDCl_3$) 1.13 (3H, s, 8-H), 1.97-2.06 (2H, m, 6,7-H), 2.15 (1H, m, 7-H), 2.48 (1H, m, 6-H), 2.78 (1H, dd, *J* 13.1 and 4.3, 2-H), 3.10 (1H, t, *J* 3.1, 7$_a$-H), 3.35 (3H, s, 10-H), 3.64 (1H, m, 2-H), 3.84 (1H, t, *J* 4.1, 3-H), 5.52 (1H, d, *J* 10.1, 4-H), 5.81-5.89 (1H, m, 5-H); δ_C (125 MHz, $CDCl_3$) 16.8 (7-C), 21.0 (8-C), 22.0 (6-C), 45.8 (3$_a$-C), 54.1 (2-C), 56.9 (10-C), 58.6 (7$_a$-C), 85.4 (3-C), 127.7 (5-C), 129.5 (4-C); *m/z* (EI) 201 (M^+H, 4%), 165 (37), 83 (61), 57 (100); HR (ESI) 201.0939 (M^+H $C_{10}H_{17}O_2S$ requires 201.0943); **92b** (minor diastereoisomer), colourless oil, υ_{max} (neat)/cm^{-1} 2923, 1050, 718; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, s, 8-H), 1.96-2.07 (2H, m, 6,7-H), 2.17-2.29 (1H, m, 7-H), 2.48 (1H, m, 6-H), 2.81 (1H, dd, *J* 12.8 and 8.1, 2-H), 2.95 (1H, t, *J* 5.0, 7$_a$-H), 3.39 (3H, s, 10-H), 3.40-3.49 (1H, m, 3-H), 3.74 (1H, dd, *J* 12.8 and 5.2, 2-H), 5.67 (1H, d, *J* 10.2, 4-H), 5.95 (1H, m, 5-H); δ_C (100 MHz, $CDCl_3$) 18.2 (7-C), 23.6 (6-C), 27.0 (8-C), 46.5 (3$_a$-C), 54.8 (2-C), 59.0 (10-C), 61.8 (7$_a$-C), 86.5 (3-C), 128.0 (5-C), 129.4 (4-C); *m z* (EI) 201 (M^+H, 10%), 165 (56), 83 (100), 57 (80); HR (ESI) 201.0946 (M^+H $C_{10}H_{17}O_2S$ requires 201.0943).

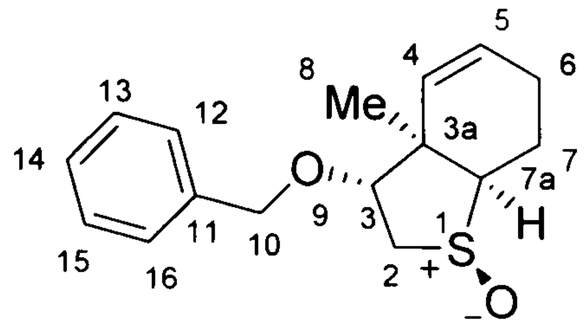
Method B: **92a** from **91a**.

To a stirred suspension of sodium hydride (1.5 mmol) in dry THF (3 cm^3) at 0 °C was added dropwise a solution of *rel*-(1*S*,3*R*,3$_a$*R*,7$_a$*R*)-3$_a$-methyl-1-oxo-2,3,3$_a$,6,7,7$_a$-hexahydro-1*H*-1λ^4-benzo[*b*]thiophen-3-ol **91a** (0.260 g, 1.4 mmol) in THF (8 cm^3). Methyl iodide (0.087 cm^3, 1.4 mmol) was added after 2 h at 0 °C. The reaction was allowed to warm to room temperature overnight. The reaction was then quenched with distilled water (20 cm^3) and the aqueous layer was extracted with diethyl ether (3×20 cm^3). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by column chromatography (4% MeOH in diethyl ether) to afford the title compound **92a** (0.066 g, 22%), *data as above*.

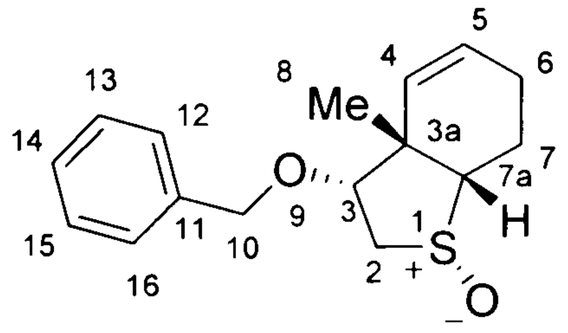
Method B: **92b** from **91b**.

To a stirred suspension of sodium hydride (1.7 mmol) in dry THF (3 cm^3) at 0 °C was added dropwise a solution of *rel*-(1*R*,3*R*,3$_a$*S*,7$_a$*S*)-3$_a$-methyl-1-oxo-2,3,3$_a$,6,7,7$_a$-hexahydro-1*H*-1λ^4-benzo[*b*]thiophen-3-ol **91b** (0.29 g, 1.6 mmol) in THF (10 cm^3). Methyl iodide (0.10 cm^3, 1.6 mmol) was added after 2 h at 0 °C. The reaction was allowed to warm to room temperature overnight. The reaction was then quenched with distilled water (20 cm^3) and the aqueous layer was extracted with diethyl ether (3×20 cm^3). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by column chromatography (diethyl ether) to afford the title compound **92b** (0.12 g, 35%), *data as above*.

Rel-(1_S_,3_R_,3$_a$_R_,7$_a$_R_)-3-benzyloxy-3$_a$-methyl-2,3,3$_a$,6,7,7a-hexahydro-benzo[_b_]thiophene-1-oxide (93a) and _rel_-(1_R_,3_R_,3$_a$_S_,7$_a$_S_)-3-benzyloxy-3$_a$-methyl-2,3,3$_a$,6,7,7$_a$-hexahydro-benzo[_b_]thiophene-1-oxide (93b)



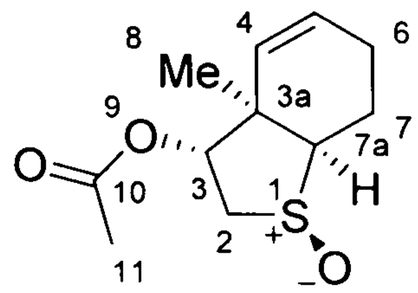
93a



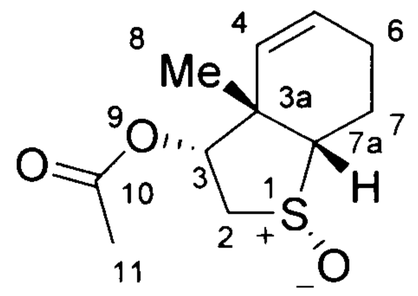
93b

A solution of _rel_-(1_R_)-1-(1-methyl-cyclohexa-2.5-dienyl)-1-benzyloxy-2-((_R_)-_t_-butylsulfinyl)-ethane **93** (0.126 g, 0.38 mmol) was placed under an inert atmosphere of argon and refluxed in xylene (0.14 M) for 1 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by column chromatography (diethyl ether) afforded starting material (0.02 g, 16%) followed by a mixture of cycloadducts **93a** and **93b** as a colourless oil (0.087 g, 83%, dr 3.6:1), R_f=1.5 (diethyl ether); **93a** (major diastereoisomer), υ_{max} (neat)/cm^{-1} 1454, 1099, 1043; δ_H (400 MHz, $CDCl_3$) 1.18 (3H, s, 8-H), 1.94-2.09 (2H, m, 6,7-H), 2.15-2.19 (1H, m, 7-H), 2.48-2.51 (1H, m, 6-H), 2.85 (1H, dd, _J_ 13.1 and 4.2, 2-H), 3.18 (1H, t, _J_ 5.2, 7$_a$-H), 3.65 (1H, dd, _J_ 13.1 and 3.9, 2-H), 4.02 (1H, t, _J_ 4.1, 3-H), 4.45-4.66 (2H, m, 10-H), 5.53 (1H, d, _J_ 10.1, 4-H), 5.83-5.88 (1H, m, 5-H), 7.26-7.38 (5H, m, 12-16-H); δ_C (100 MHz, $CDCl_3$) 18.1 (7-C), 22.7 (8-C), 23.4 (6-C), 47.4 (3$_a$-C), 56.2 (2-C), 60.1 (7$_a$-C), 72.4 (10-C), 127.9 (13,15-C), 128.3 (14-C), 128.9 (12,16-C), 129.2 (4-C), 130.8 (5-C), 138.0 (11-C); _m/z_ (EI) 276 (M^+, 12%), 91 (100), 79 (21), 35 (30); _m/z_ (EI) 299.1078 (M^+Na $C_{16}H_{20}O_2SNa$ requires 299.1076).

***Rel*-(1*S*,3*R*,3$_a$*R*,7$_a$*R*)-acetic acid 3$_a$-methyl-1-oxo-2,3,3$_a$,6,7,7$_a$-hexahydro-1*H*-1λ^4-benzo[*b*]thiophen-3-yl ester (94a) and *rel*-(1*R*,3*R*,3$_a$*S*,7$_a$*S*)-acetic acid 3$_a$-methyl-1-oxo-2,3,3$_a$,6,7,7$_a$-hexahydro-1*H*-1λ^4-benzo[*b*]thiophen-3-yl ester (94b)**



94a

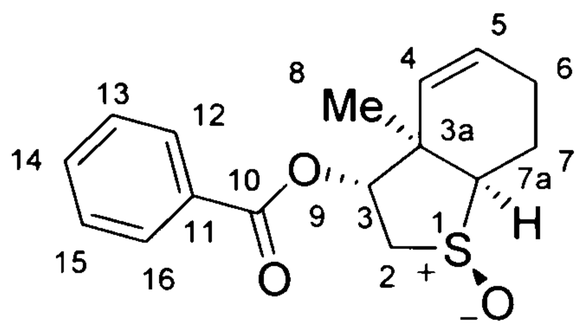


94b

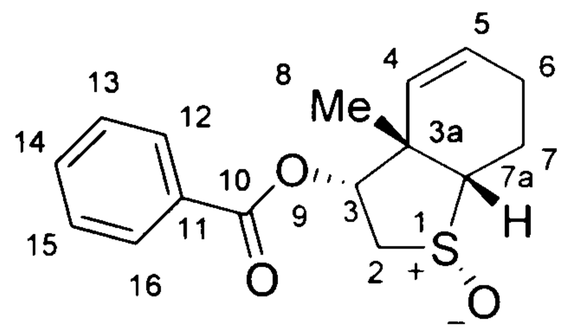
A solution of *rel*-(1*R*)-acetic acid 1-(1-methyl-cyclohexa-2,5-dienyl)-2-((*R*)-*t*-butylsulfinyl)-ethyl ester **94** (0.124 g, 0.46 mmol) was placed under an inert atmosphere of argon and refluxed in xylene (0.14 M) for 4 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by column chromatography (9:1 diethyl ether/60-80 °C petroleum ether) afforded the *title compound* **94a** as a colourless oil (0.056 g, 53%) followed by the *title compound* **94b** as a colourless oil (0.028 g, 27%). **94a** R_f=0.25 (9:1 diethyl ether/60-80 °C petroleum ether); υ_{max} (neat)/cm^{-1} 1744, 1233, 1046; δ_H (360 MHz, $CDCl_3$) 1.09 (3H, s, 8-H), 1.94-2.09 (2H, m, 6,7-H), 2.03 (3H, s, 11-H), 2.22-2.30 (1H, m, 7-H), 2.46-2.57 (1H, m, 6-H), 2.97 (1H, dd, *J* 13.6 and 4.5, 2-H), 3.11 (1H, t, *J* 4.5, 7$_a$-H), 3.59 (1H, dd, *J* 13.5 and 2.6, 2-H), 5.32 (1H, dd, *J* 4.4 and 2.8, 3-H), 5.50 (1H, m, 4-H), 5.90 (1H, m, 5-H); δ_C (100 MHz, $CDCl_3$) 17.3 (7-C), 20.7 (8-C), 22.2 (11-C), 22.5 (6-C), 46.2 (3$_a$-C), 57.4 (2-C), 59.2 (7$_a$-C), 79.7 (3-C), 128.6 (4-C), 130.0 (5-C), 169.7 (10-C); *m/z* (FAB) 229 (M^+H, 100%), 169 (23), 119 (25), 91 (27); HR (FAB) 229.0903 (M^+H $C_{11}H_{17}O_3S$ requires 229.0898); **94b** R_f=0.2 (9:1 diethyl ether/60-80 °C petroleum ether); υ_{max} (neat)/cm^{-1} 1750, 1217, 1020; δ_H (360 MHz, $CDCl_3$) 1.08 (3H, s, 8-H), 1.97-2.06 (1H, m, 7-H), 2.08 (3H, s, 11-H), 2.12-2.15 (1H, m, 6-H), 2.17-2.24 (1H, m, 7-H), 2.44-2.49 (1H, m, 6-H), 2.84 (1H, dd, *J* 14.0 and 5.7, 2-H), 3.14 (1H, dd, *J* 9.2 and 4.9, 7$_a$-H), 3.83 (1H, dd, *J* 14.0 and 5.8, 2-H), 5.03 (1H, t, *J* 5.8, 3-H), 5.58-5.62 (1H, m, 4-H), 5.93-5.98 (1H, m, 5-H); δ_C (100 MHz, $CDCl_3$) 17.7 (7-C), 21.1 (11-C), 23.4 (6-C), 26.3 (8-C), 47.0 (3$_a$-C), 55.7 (2-C), 62.3 (7$_a$-C), 77.9 (3-C), 127.5 (4-C), 129.4 (5-C), 170.1 (10-C), *m z* (EI)

228 (M^+, 41%), 120 (58), 105 (66), 43 (100); HR (ESI) 251.0709 (M^+Na $C_{11}H_{16}O_3SNa$ requires 251.0712).

Rel-(1_S_,3_R_,3$_a$_R_,7$_a$_R_)-benzoic acid 3$_a$-methyl-1-oxo-2,3,3$_a$,6,7,7$_a$-hexahydro-1_H_-1λ^4-benzo[_b_]thiophen-3-yl ester (95a) and _rel_-(1_R_,3_R_,3$_a$_S_,7$_a$_S_)-benzoi acid 3$_a$-methyl-1-oxo-2,3,3$_a$,6,7,7$_a$-hexahydro-1_H_-1λ^4-benzo[_b_]thiophen-3-yl ester (95b)



95a



95b

A solution of _rel_-(1_R_)-benzoic acid 1-(1-methyl-cyclohexa-2,5-dienyl)-2-((_R_)-_t_-butylsulfinyl)-ethyl ester **95** (0.067 g, 0.19 mmol) was placed under an inert atmosphere of argon and refluxed in xylene (0.14 M) for 2.5 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by column chromatography (diethyl ether) afforded the *title compound* **95a** as a colourless oil (0.027 g, 49%) followed by the *title compound* **95b** as a colourless oil (0.014 g, 25%), **95a** R_f=0.25 (diethyl ether); υ_{max} (neat)/cm^{-1} 2916, 1715, 1268, 1110, 1018; δ_H (500 MHz, $CDCl_3$) 1.23 (3H, s, 8-H), 2.05-2.13 (2H, m, 6,7-H), 2.34-2.40 (1H, m, 7-H), 2.57-2.64 (1H, m, 6-H), 3.14 (1H, dd, _J_ 9.2 and 4.3, 2-H), 3.29 (1H, t, _J_ 4.5, 7$_a$-H), 3.77 (1H, dd, _J_ 11.0 and 2.5, 2-H), 5.61-5.65 (2H, m, 4,3-H), 5.98 (1H, m, 5-H), 7.45-7.97 (5H, m, 12-16-H); δ_C (125 MHz, $CDCl_3$) 17.5 (7-C), 22.6 (8-C), 22.7 (6-C), 46.7 (3$_a$-C), 57.6 (2-C), 59.6 (7$_a$-C), 80.4 (3-C), 128.6 (13,15-C), 128.7 (4-C), 129.2 (11-C), 129.6 (12,16-C), 130.2 (4-C), 133.6 (5-C), 165.2 (10-C); _m/z_ (EI) 290 (M^+, 15%), 205 (90), 105 (100), 77 (28); HR (ESI) 291.1042 (M^+H $C_{16}H_{19}O_3S$ requires 291.1049); **95b** R_f=0.2 (diethyl ether); υ_{max} (neat)/cm^{-1} 2922, 1718, 1269, 1046, 963; δ_H (500 MHz, $CDCl_3$) 1.16 (3H, s, 8-H), 2.04-2.17 (2H, m, 6,7-H), 2.27-2.35 (1H, m, 7-H), 2.44-2.50 (1H, m, 6-H), 3.00 (1H, dd, _J_ 5.4 and 8.7, 2-H), 3.18 (1H, dd, _J_ 4.6 and 5.0, 7$_a$-H), 3.93 (1H, dd, _J_ 5.8 and 8.3, 2-H), 5.30 (1H, t, _J_ 5.6, 3-H), 5.71 (1H, m, 4-H), 5.94

(1H, m, 5-H), 7.57-8.02 (5H, m, 12-16-H); δ_C (125 MHz, $CDCl_3$) 18.4 (7-C), 23.8 (6-C), 27.0 (8-C), 47.7 (3_a-C), 56.3 (2-C), 62.9 (7_a-C), 79.0 (3-C), 120.0 (14-C), 128.9 (13,15-C), 129.6 (11-C), 129.9 (4-C), 129.9 (12,16-C), 133.8 (5-C), 165.9 (10-C); *m/z* (EI) 290 (M^+, 16%), 205 (29), 105 (100), 77 (37); HR (ESI) 291.1056 (M^+H $C_{16}H_{19}O_3S$ requires 291.1049).

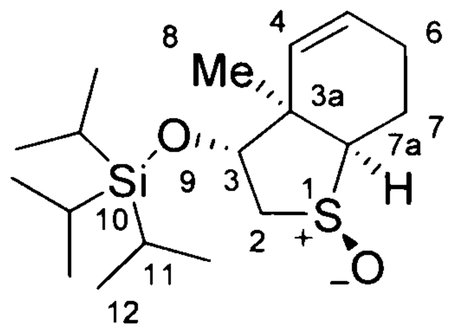
Method B: from **95a**.

A solution of *rel*-(1*S*,3*R*,3$_a$*R*,7$_a$*R*)-benzoic acid 3$_a$-methyl-1-oxo-2,3,3$_a$,6,7,7$_a$-hexahydro-1*H*-1λ^4-benzo[*b*]thiophen-3-yl ester **95a** (0.039 g, 0.13 mmol) was placed under an inert atmosphere of argon and refluxed in xylene (0.14 M) for 2 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by column chromatography (diethyl ether) afforded the title compound **95a** (0.02 g, 53%) followed by the title compound **95b** (0.011 g, 29%), *data as above*.

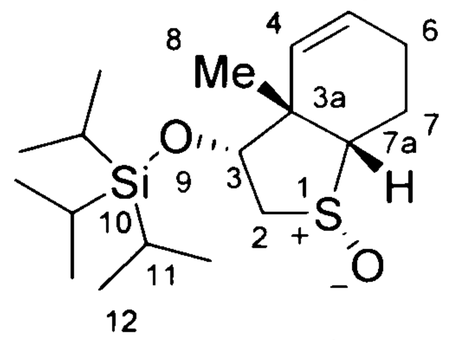
Method C: from **95b**.

A solution of *rel*-(1*R*,3*R*,3$_a$*S*,7$_a$*S*)-benzoic acid 3$_a$-methyl-1-oxo-2,3,3$_a$,6,7,7$_a$-hexahydro-1*H*-1λ^4-benzo[*b*]thiophen-3-yl ester **95b** (0.018 g, 0.062 mmol) was placed under an inert atmosphere of argon and refluxed in xylene (0.14 M) for 2 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by column chromatography (diethyl ether) afforded the title compound **95a** (0.01 g, 56%) followed by the title compound **95b** (0.005 g, 28%), *data as above*.

Rel-(1*S*,3*R*,3$_a$*R*,7$_a$*R*)-3-(tri-isopropylsilyl)oxy-3$_a$-methyl-2,3,3$_a$,6,7,7$_a$-hexahydro-benzo[*b*]thiophen-1-oxide (96a) and _rel_-(1*R*,3*R*,3$_a$*S*,7$_a$*S*)-3-(tri-isopropylsilyl)oxy-3$_a$-methyl-2,3,3$_a$,6,7,7$_a$-hexahydro-benzo[*b*]thiophen-1-oxide (96b)



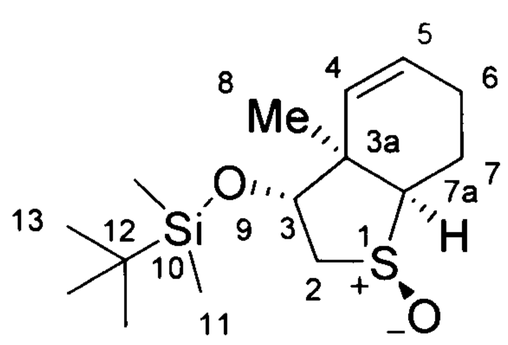
96a



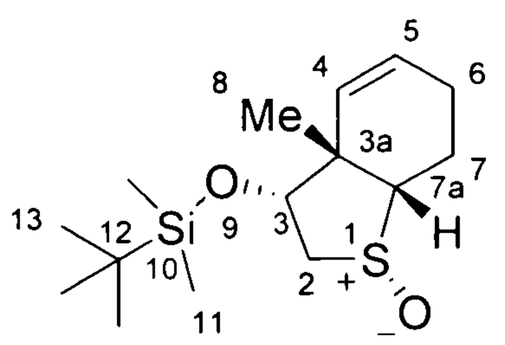
96b

A solution of *rel*-(1*R*)-1-(1-methyl-cyclohexa-2,5-dienyl)-1-(tri-isopropylsilyl)oxy-2-((*R*)-*t*-butylsulfinyl)-ethane **96** (0.054 g, 0.14 mmol) was placed under an inert atmosphere of argon and refluxed in xylene (0.14 M) for 2 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by column chromatography (1:1 diethyl ether/60-80 °C petroleum ether) afforded the mixture of the *title compounds* **96a** and **96b** as a colourless oil (0.028 g, 45%, dr 4.3:1). R_f=0.3 (5:5 diethyl ether/60-80 °C petroleum ether); **96a** (major diastereoisomer). υ_{max} (neat)/cm^{-1} 1059, 883; δ_H (400 MHz, $CDCl_3$) 1.08 (21H, s, 11,12-H), 1.16 (3H, s, 8-H), 2.05-2.57 (3H, m, 6,7-H), 2.58 (1H, m, 6-H), 2.86 (1H, dd, *J* 3.9 and 13.8, 7-H), 2.91 (1H, dd, *J* 4.1 and 13.2, 2-H), 3.18 (1H, t, *J* 5.3, 7$_a$-H), 3.52 (1H, dd, *J* 3.5 and 9.1, 2-H), 4.45 (1H, t, *J* 4.0, 3-H), 5.53 (1H, d, *J* 10.3, 4-H), 5.85 (1H, m, 5-H); δ_C (100 MHz, $CDCl_3$) 12.6 (11-C), 18.2 (7-C), 18.5 (12-C), 23.0 (8-C), 23.6 (6-C), 48.5 (3$_a$-C), 59.5 (7$_a$-C), 60.1 (2-C), 79.9 (3-C), 129.0 (5-C), 131.0 (4-C); *m/z* (EI) 342 (M$^+$, 9%), 299 (22), 49 (100); HR (ESI) 365.1948 (M$^+$Na $C_{18}H_{34}O_2SSiNa$ requires 365.1941).

Rel-(1_S_,3_R_,3$_a$_R_,7$_a$_R_)-3-(_tert_-butyl-dimethylsilyl)oxy-3$_a$-methyl-2,3,3$_a$,6,7,7$_a$-hexahydro-benzo[_b_]thiophene-1-oxide (97a) and _rel_-(1_R_,3_R_,3$_a$_S_,7$_a$_S_)-(_tert_-butyl-dimethylsilyl)oxy-3$_a$-methyl-2,3,3$_a$,6,7,7$_a$-hexahydro-benzo[_b_]thiophene-1-oxide (97b)



97a



97b

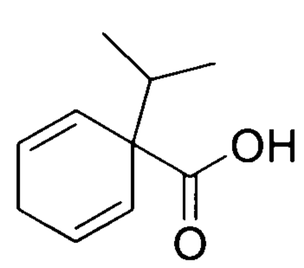
A solution of _rel_-(1_R_)-1-(1-methyl-cyclohexa-2,5-dienyl)-1-(_t_-butyl-dimethylsilyl)oxy-2-((_R_)-_t_-butylsulfinyl)-ethane **97** (0.117 g, 0.33 mmol) was placed under an inert atmosphere of argon and refluxed in xylene (0.14 M) for 2.5 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by column chromatography (3:2 diethyl ether/60-80 °C petroleum ether) afforded the *title compound* **97a** as a colourless oil (0.049 g, 49%), followed by the *title compound* **97b** as a colourless oil (0.010 g, 10%). **97a** R_f=0.3 (3:2 diethyl ether/60-80 °C petroleum ether); υ_{max} (neat)/cm^{-1} 1443, 1058; δ_H (360 MHz, $CDCl_3$) 0.06 (3H, s, 11-H), 0.08 (3H, s, 11-H), 0.86 (9H, s, 13-H), 1.09 (3H, s, 8-H), 1.87-2.08 (2H, m, 6,7-H), 2.20 (1H, m, 7-H), 2.50 (1H, m, 6-H), 2.86 (1H, dd, _J_ 3.8 and 8.8, 2-H), 3.15 (1H, t, _J_ 5.1, 7$_a$-H), 3.44 (1H, dd, _J_ 3.5 and 9.1, 2-H), 4.20 (1H, t, _J_ 3.6, 3-H), 5.30 (1H, m, 4-H), 5.84 (1H, m, 5-H); δ_C (100 MHz, $CDCl_3$) 18.1 (7-C), 18.3 (12-C), 23.0 (8-C), 23.4 (6-C), 26.0 (13-C), 48.0 (3$_a$-C), 59.4 (7$_a$-C), 61.5 (2-C), 79.5 (3-C), 129.2 (5-C), 130.7 (4-C); _m/z_ (EI) 300 (M$^+$, 15%), 243 (38), 149 (100), 73 (48); HR (ESI) 301.1652 (M$^+$H $C_{15}H_{29}O_2SSi$ requires 301.1652); **97b** R_f=0.2 (3:2 diethyl ether/60-80 °C petroleum ether); υ_{max} (neat)/cm^{-1} 1443, 1114; δ_H (360 MHz, $CDCl_3$) 0.08 (6H, s, 11-H), 0.91 (9H, s, 13-H), 1.08 (3H, s, 8-H), 2.01-2.09 (2H, m, 6,7-H), 2.34 (1H, m, 7-H), 2.55 (1H, m, 6-H), 2.76 (1H, dd, _J_ 2.7 and 9.6, 2-H), 2.85 (1H, t, _J_ 5.0, 7$_a$-H), 3.63 (1H, dd, _J_ 5.5 and 6.8, 2-H), 3.72 (1H, dd, _J_ 5.4 and 4.1, 3-H), 5.73 (1H, m, 4-H), 5.94 (1H, m, 5-H); δ_C (90 MHz, $CDCl_3$) 18.2 (7-C), 18.4 (12-C), 23.6 (6-C), 26.1 (13-C), 26.4 (8-C),

46.1 (3_a-C), 58.5 (2-C), 60.7 (7_a-C), 77.2 (3-C), 127.6 (5-C), 129.5 (4-C); *m z* (EI) 300 (M^+, 12%), 243 (73), 149 (100), 73 (28); HR (ESI) 301.1653 (M^+H $C_{15}H_{29}O_2SSi$ requires 301.1652).

Method B: from **97a**.

A solution of *rel*-(1*S*,3*R*,3$_a$*R*,7$_a$*R*)-3-(*tert*-butyl-dimethylsilyl)oxy-3$_a$-methyl-2,3,3$_a$,6,7,7$_a$-hexahydro-benzo[*b*]thiophene-1-oxide **97a** (0.063 g, 0.21 mmol) was placed under an inert atmosphere of argon and refluxed in xylene (0.14 M) for 2.5 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by column chromatography (diethyl ether) afforded a mixture of the title compounds **97a** and **97b** as a colourless oil (0.044 g, 70%, dr 5:1), *data as above*.

1-Isopropyl-cyclohexa-2,5-diene-1-carboxylic acid (105)[63]

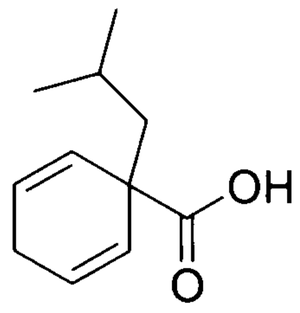


105

Ammonia (150 cm^3) was added to benzoic acid (2.50 g, 20.5 mmol) with careful stirring. To this, sodium (1.40 g, 61.4 mmol) was added portionwise until a permanent blue colour persisted, followed by dropwise addition of 2-bromopropane (7.0 cm^3, 61.4 mmol). The reaction mixture was left for 1 h, whilst the ammonia evaporated, and ice was added to the remaining solid, followed by dilute H_2SO_4. The product was extracted with diethyl ether (3×50 cm^3) and the combined ethereal extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The crude compound was purified by column chromatography (1:4 diethyl ether/60-80 °C petroleum ether) to afford the title compound **105** as a colourless oil (2.1 g, 62%), R_f=0.2 (1:4 diethyl ether/60-80 °C petroleum ether); δ_H (360 MHz, $CDCl_3$) 0.87 (6H, d, *J* 6.9, 2×C*H*$_3$), 2.07-2.19 (1H, septet, *J* 6.9, CH_3CH), 2.64 (2H, m, $CHCH_2CH$), 5.73-5.78 (2H, m, 2×CHC*H*), 5.94-5.98 (2H, m, 2×CHC*H*), 11.0 (1H, bs,

COO*H*); δ_C (90 MHz, $CDCl_3$) 17.7 (2×q), 26.9 (t), 35.6 (d), 52.2 (s), 48.0 (s), 125.6 (d), 127.3 (d), 128.9 (d), 130.7 (d), 181.7 (s).

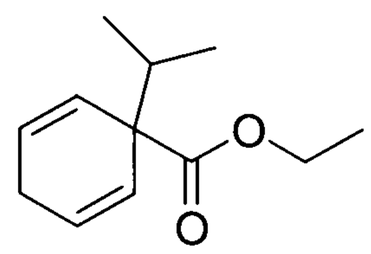
1-Isobutyl-cyclohexa-2,5-diene-1-carboxylic acid (106)[63]



106

Ammonia (150 cm^3) was added to benzoic acid (2.50 g, 20.5 mmol) with careful stirring. To this, sodium (1.40 g, 61.4 mmol) was added portionwise until a permanent blue colour persisted, followed by dropwise addition of 1-iodo-2-methylpropane (7.0 cm^3, 61.4 mmol). The reaction mixture was left for 1 h, whilst the ammonia evaporated, and ice was added to the remaining solid, followed by dilute H_2SO_4. The product was extracted with diethyl ether (3×50 cm^3) and the combined ethereal extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The crude compound was purified by column chromatography (1:4 diethyl ether/60-80 °C petroleum ether) to afford the title compound **106** as a white solid (2.06 g, 56%), R_f=0.2 (1:4 diethyl ether/60-80 °C petroleum ether): δ_H (360 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.3, CH_3), 0.90 (3H, d, *J* 6.6, CH_3), 1.68-1.81 (3H, m, CH_3CHCH_2,CH_3CHCH_2), 2.66 (2H, d, *J* 1.6, CHCH_2CH), 5.73-5.82 (2H, m, 2×CHC*H*), 5.84-5.91 (2H, m, 2×CHC*H*), 11.0 (1H, bs, COO*H*); δ_C (90 MHz, $CDCl_3$) 23.2 (q), 24.6 (d), 25.2 (q), 26.4 (t), 48.0 (s), 48.5 (t), 126.0 (d), 126.9 (d), 127.8 (d), 131.1 (d).

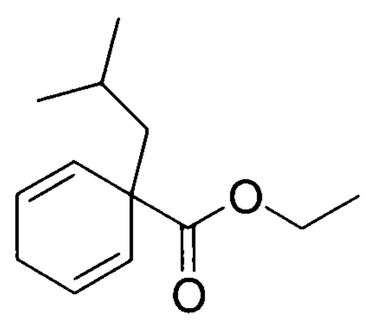
1-Isopropyl-cyclohexa-2,5-dienecarboxylic acid ethyl ester (107)



107

Potassium carbonate (4.3 g, 31.3 mmol) and iodoethane (4.0 cm^3, 48.4 mmol) were added to a solution of 1-isopropylcyclohexa-2,5-diene-1-carboxylic acid **105** (2.08 g, 12.5 mmol) in acetone (36 cm^3) and distilled water (1.9 cm^3), and the mixture was heated to 75 °C. After 3 h, the reaction was cooled to room temperature, diluted with distilled water (50 cm^3) and 10% HCl (4.8 cm^3), extracted with dichloromethane (3×50 cm^3), washed with saturated NaCl (100 cm^3), dried over $MgSO_4$ and evaporated *in vacuo* to afford the *title compound* **107** as a colourless oil (2.1 g, 88%), R_f=0.3 (1:4 diethyl ether/60-80 °C petroleum ether); υ_{max} (neat)/cm^{-1} 2965, 1726, 1386, 1254; δ_H (360 MHz, $CDCl_3$) 0.83 (6H, d, *J* 6.9, 2×CH_3CH), 1.26 (3H, t, *J* 7.1, CH_3CH_2), 2.10 (1H, septet, *J* 7.0, CH_3CH), 2.62 (2H, m, CHCH_2CH), 4.15 (2H, q, *J* 7.1, CH_3CH_2), 5.73-5.78 (2H, m, 2×CHC*H*), 5.90-5.94 (2H, m, 2×CHC*H*); δ_C (90 MHz, $CDCl_3$) 14.6 (q), 17.7 (2×q), 26.9 (t), 36.2 (d), 52.2 (s), 61.0 (t), 126.3 (d), 126.7 (d), 128.7(d), 130.0 (d), 175.3 (s); *m/z* (EI) 194 (M^+, 22%), 151 (53), 105 (52), 79 (100); HR (ESI) 217.1197 (M^+Na $C_{12}H_{18}O_2Na$ requires 217.1199).

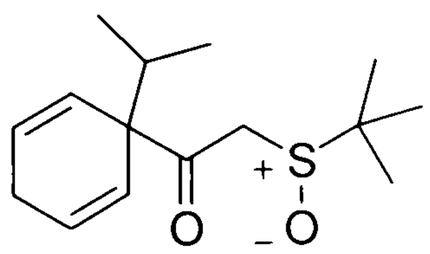
1-Isobutyl-cyclohexa-2,5-dienecarboxylic acid ethyl ester (108)



108

Potassium carbonate (4.2 g, 30.3 mmol) and iodoethane (3.9 cm^3, 48.4 mmol) were added to a solution of 1-isobutylcyclohexa-2,5-diene-1-carboxylic acid **106** (2.01 g, 11.0 mmol) in acetone (35 cm^3) and distilled water (1.8 cm^3), and the mixture was heated to 75 °C. After 3 h, the reaction was cooled to room temperature, diluted with distilled water (50 cm^3) and 10% HCl (4.6 cm^3), extracted with dichloromethane (3×50 cm^3), washed with saturated NaCl (100 cm^3), dried over $MgSO_4$ and evaporated *in vacuo* to afford the *title compound* **108** as a colourless oil (2.20 g, 96%), R_f=0.3 (1:4 diethyl ether/60-80 °C petroleum ether); υ_{max} (neat)/cm^{-1} 2958, 1726.2, 1467, 1234; δ_H (360 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.5, CH_3CHCH_2), 0.91 (3H, d, *J* 6.5, CH_3CHCH_2), 1.26 (3H, t, *J* 7.2, CH_3CH_2), 1.61-1.73 (3H, m, CH_3CHCH_2,CH_3CHCH_2), 2.64 (2H, d, *J* 1.5, $CHCH_2CH$), 4.12 (2H, q, *J* 7.1, CH_3CH_2), 5.74-5.87 (4H, m, 2×*CHCH*); δ_C (90 MHz, $CDCl_3$) 14.5 (q), 23.2 (q), 24.6 (d), 25.1 (q), 26.5 (t), 48.1 (s), 48.9 (t), 61.2 (t), 125.3 (d), 127.7 (d), 128.5(d), 130.4 (d), 175.6 (s).

1-(1-Isopropyl-cyclohexa-2,5-dienyl)-2-(*t*-butylsulfinyl)-ethanone (109)

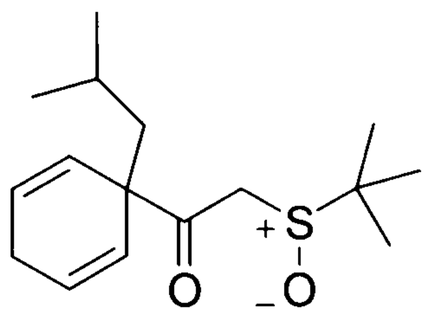


109

To a solution of lithium diisopropylamide (23.5 mmol) in dry THF (23 cm^3) at -78 °C was added dropwise a solution of *t*-butyl methyl sulfoxide **75** (2.57 g, 21.4 mmol) in THF

(5 cm^3). The reaction was stirred for 2 h. 1-Isopropyl-cyclohexa-2,5-dienecarboxylic acid **107** ethyl ester (2.08 g, 10.7 mmol) was then added and the reaction was stirred at -78 °C for a further 3 h. The reaction was then allowed to warm to room temperature, quenched with saturated NH_4Cl (40 cm^3) and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3×40 cm^3) and the combined organic extracts were washed with saturated NaCl (50 cm^3), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (diethyl ether) to afford the *title compound* **109** as a pale yellow oil (1.15 g, 40%), R_f=0.3 (diethyl ether); υ_{max} (neat)/cm^{-1} 2963, 1703, 1464, 1367, 1040; δ_H (360 MHz, $CDCl_3$) 0.84 (6H, dd, *J* 1.9 and 6.8, 2×CH_3CH), 1.25 (9H, s, (CH_3)$_3$CS), 2.30 (1H, septet, *J* 6.9, CH_3C*H*), 2.75 (2H, m, CHCH_2CH), 3.67 (2H, d, *J* 1.1, CH_2S), 5.58 (2H, m, 2×C*H*CH), 6.07 (2H, m, 2×C*H*CH); δ_C (90 MHz, $CDCl_3$) 15.7 (s), 18.0 (q), 18.1 (q), 23.2 (3×q), 27.1 (t), 33.4 (d), 54.5 (s), 57.2 (t), 125.8 (d), 126.0 (d), 129.1 (d), 129.2 (d), 204.2 (s); *m/z* (ESI) 269 (M^+, 51%), 161 (13); HR (ESI) 291.1379 (M^+Na $C_{15}H_{24}O_2SNa$ requires 291.1389).

1-(1-Isobutyl-cyclohexa-2,5-dienyl)-2-(*t*-butylsulfinyl)-ethanone (110)

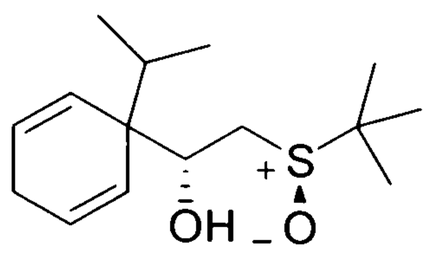


110

To a solution of lithium diisopropylamide (15.0 mmol) in dry THF (15 cm^3) at -78 °C was added dropwise a solution of *t*-butyl methyl sulfoxide **75** (1.56 g, 13 mmol) in THF (3 cm^3). The reaction was stirred for 2 h. 1-Isobutyl-cyclohexa-2,5-dienecarboxylic acid ethyl ester **108** (1.26 g, 6.1 mmol) was then added and the reaction was stirred at -78 °C for a further 3 h. The reaction was then allowed to warm to room temperature, quenched with saturated NH_4Cl (20 cm^3) and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3×20 cm^3) and the combined organic extracts were washed with saturated NaCl (30 cm^3), dried over $MgSO_4$ and concentrated *in vacuo*. The

crude product was purified by column chromatography (diethyl ether) to afford the *title compound* **110** as a pale yellow oil (0.77 g, 45%). R_f=0.3 (diethyl ether); υ_{max} (neat)/cm^{-1} 2956, 1706, 1466, 1366, 1120; δ_H (360 MHz, $CDCl_3$) 0.88 (6H, d, *J* 6.3, 2×CH_3CHCH$_2$), 1.24 (9H, s, (CH_3)$_3$CS), 1.59-1.70 (3H, m, CH$_3$C*H*CH$_2$,CH_3CHCH_2), 2.73-2.89 (2H, m, CHCH_2CH), 3.69 (2H, d, *J* 8.3, CH_2S), 5.53 (2H, m, 2×C*H*CH), 6.01 (2H, m, 2×C*H*CH); δ_C (90 MHz, $CDCl_3$) 23.2 (3×q), 24.8 (2×q), 25.1 (d), 26.7 (t), 44.6 (t), 54.5 (s), 56.0 (t), 127.9 (d), 128.0 (d), 128.1 (d), 128.2 (d); *m/z* (EI) 283 (M^+, 35%), 135 (100), 79 (44), 57 (99); HR (ESI) 305.1547 (M^+Na $C_{16}H_{26}O_2SNa$ requires 305.1546).

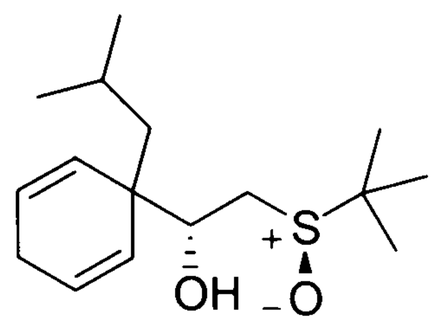
Rel-(1_R_)-1-(1-isopropyl-cyclohexa-2,5-dienyl)-2-((_R_)-_t_-butylsulfinyl)-ethanol (111)



111

To a solution of 1-(1-isopropyl-cyclohexa-2,5-dienyl)-2-(*t*-butylsulfinyl)-ethanone **109** (1.16 g, 4.3 mmol) in dry THF (45 cm^3) at –78 °C was added dropwise a 1M solution of diisobutylaluminum hydride in toluene (4.7 cm^3, 4.7 mmol). After 3 h at –78 °C, methanol (45 cm^3) was added to the reaction vessel. The solvent was then evaporated *in vacuo* and the residue diluted with distilled water (70 cm^3) and extracted with dichloromethane (3×80 cm^3). The organic layer was then washed with a 5% NaOH solution (100 cm^3), dried over $MgSO_4$ and evaporated *in vacuo* to afford the *title compound* **111** as a white solid (0.92 g, 80%). R_f=0.1 (diethyl ether); mp 128 °C; υ_{max} (neat)/cm^{-1} 3436, 2926, 1632, 1463, 1070, 1006; δ_H (360 MHz, $CDCl_3$) 0.82 (3H, d, *J* 6.9, CH_3CH), 0.94 (3H, d, *J* 6.8, CH_3CH), 1.23 (9H, s, (CH_3)$_3$CS), 1.98 (1H, septet, *J* 6.9, CH$_3$C*H*), 2.60 (4H, m, CHCH_2CH, CH_2S), 3.06 (1H, bs, OH), 4.27 (1H, bs, C*H*OH), 5.37 (1H, d, *J* 9.4, C*H*CH), 5.60 (1H, d, *J* 9.6, C*H*CH), 5.94 (2H, m, 2×C*H*CH); δ_C (100 MHz, $CDCl_3$) 17.1 (q), 18.6 (q), 23.4 (3×q), 27.7 (t), 30.1 (t), 32.6 (d), 48.0 (s), 69.2 (d), 126.7 (d), 127.5 (d), 128.4 (d), 128.6 (d); *m z* (EI) 271 (M^+, 5%), 148 (52), 121 (50), 57 (100); HR (ESI) 293.1510 (M^+Na $C_{15}H_{26}O_2SNa$ requires 293.1545).

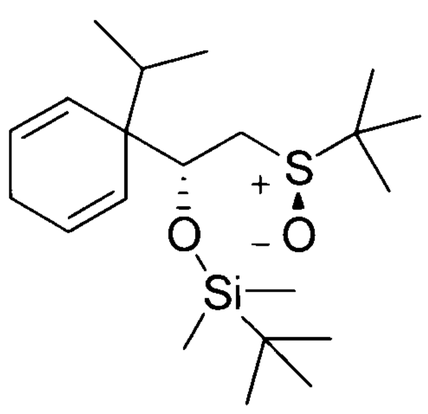
Rel-(1*R*)-1-(1-isobutyl-cyclohexa-2,5-dienyl)-2-((*R*)-*t*-butylsulfinyl)-ethanol (112)



112

To a solution of 1-(1-isobutyl-cyclohexa-2,5-dienyl)-2-(*t*-butylsulfinyl)-ethanone **110** (0.77 g, 1.7 mmol) in dry THF (30 cm^3) at –78 °C was added dropwise a 1M solution of diisobutylaluminum hydride in toluene (3 cm^3, 3 mmol). After 3 h at –78 °C, methanol (30 cm^3) was added to the reaction vessel. The solvent was then evaporated *in vacuo* and the residue diluted with distilled water (50 cm^3) and extracted with dichloromethane (3×50 cm^3). The organic layer was then washed with a 5% NaOH solution (50 cm^3), dried over $MgSO_4$ and evaporated *in vacuo* to afford the *title compound* **112** as a white solid (0.66 g, 86%). R_f=0.1 (diethyl ether); mp 127 °C; υ_{max} (neat)/cm^{-1} 3434, 2923, 1633, 1463, 1012; δ_H (360 MHz, $CDCl_3$) 0.86 (6H, d, *J* 6.5, 2×C*H*$_3$CHCH$_2$), 1.23 (9H, s, (C*H*$_3$)$_3$CS), 1.65 (3H, m, CH$_3$C*H*CH$_2$,CH$_3$CHC*H*$_2$), 2.45-2.73 (4H, m, CHC*H*$_2$CH,C*H*$_2$S), 3.37 (1H, d, *J* 4.2, OH), 3.89 (1H, m, C*H*OH), 5.45 (1H, dd, *J* 2.0 and 10.2, C*H*CH), 5.61 (1H, dd, *J* 2.0 and 10.2, C*H*CH), 5.90 (2H, m, 2×C*H*CH); δ_C (90 MHz, $CDCl_3$) 23.0 (3×q), 24.6 (q), 24.8 (q), 25.2 (d), 26.9 (t), 45.5 (s), 46.4 (t), 48.8 (t), 52.7 (s), 72.3 (d), 126.5 (d), 126.6 (d), 129.1 (d), 130.2 (d); *m/z* (EI) 285 (M^+, 15%), 148 (100), 106 (48), 57 (93); HR (ESI) 307.1713 (M^+Na $C_{16}H_{28}O_2SNa$ requires 307.1702).

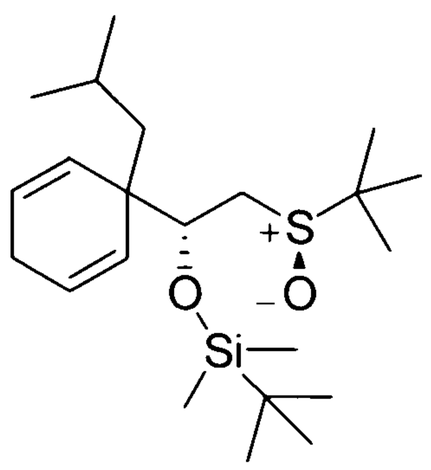
Rel-(1_R_)-1-(1-isopropyl-cyclohexa-2,5-dienyl)-1-(_t_-butyl-dimethylsilyl)oxy-2-((_R_)-_t_-butylsulfinyl)-ethane (113)



113

To a stirred solution of *rel*-(1*R*)-1-(1-isopropyl-cyclohexa-2,5-dienyl)-2-((*R*)-*t*-butylsulfinyl)-ethanol **111** (0.409 g, 1.5 mmol) and imidazole (0.20 g, 2.9 mmol) in anhydrous *N*,*N*-dimethylformamide (1.5 cm^3) was added a solution of *t*-butyldimethylsilyl chloride (0.44 g, 2.9 mmol) in *N*,*N*-dimethylformamide (1 cm^3). The solution was stirred for 3 d at room temperature under an inert atmosphere of argon. Then distilled water (30 cm^3) was added and the aqueous layer was extracted with dichloromethane (3×25 cm^3). The combined organic layer was dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude compound was purified by column chromatography (diethyl ether) to give the *title compound* **113** as a white solid (0.045 g, 8%), R_f=0.3 (diethyl ether); υ_{max} (neat)/cm^{-1} 2928, 1470, 1253, 1090; δ_H (360 MHz, $CDCl_3$) 0.20 (6H, s, $(CH_3)_2Si$), 0.76 (3H, d, *J* 6.9, CH_3CH), 0.90 (9H, s, $(CH_3)_3CSi$), 0.91 (3H, d, *J* 2.5, CH_3CH), 1.19 (9H, s, $(CH_3)_3CS$), 1.58 (1H, septet, *J* 6.9, CH_3CH), 2.30 (1H, dd, *J* 9.1 and 13.2, CH_2S), 2.61 (2H, m, $CHCH_2CH$,CH_2S), 2.75 (1H, d, *J* 1.0, $CHCH_2CH$), 4.32 (1H, d, *J* 8.6, CHOSi), 5.38 (1H, dd, *J* 2.1 and 10.4, CHCH), 5.57 (1H, dd, *J* 2.0 and 10.3, CHCH), 5.92 (2H, m, 2×CHCH); δ_C (100 MHz, $CDCl_3$) 0.0 (2×q), 16.8 (q), 19.1 (q), 23.4 (3×q), 26.6 (3×q), 27.8 (t), 31.9 (d), 49.3 (s), 52.8 (t), 53.2 (s), 69.7 (d), 126.1 (d), 127.3 (d), 128.0 (d), 129.5 (d); *m/z* (EI) 385 (M^+, 100%), 78 (8); HR (ESI) 385.2598 (M^+Na $C_{21}H_{41}O_2SSiNa$ requires 385.2598).

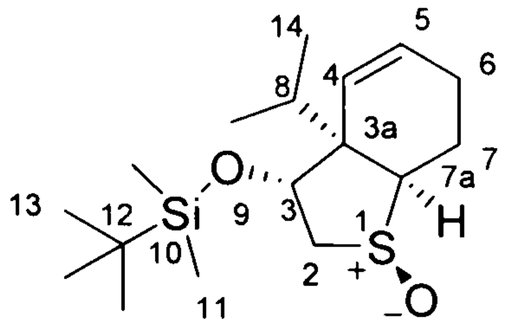
Rel-(1_R_)-1-(1-isobutyl-cyclohexa-2,5-dienyl)-1-(_t_-butyl-dimethylsilyl)oxy-2-((_R_)-_t_-butylsulfinyl)-ethane (114)



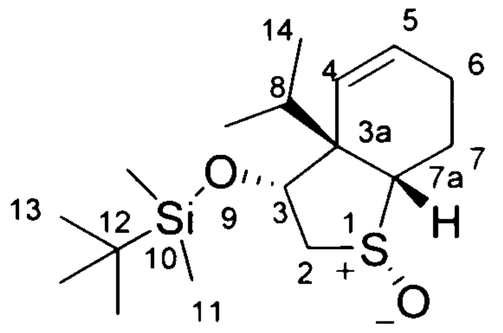
114

To a stirred solution of *rel*-(1*R*)-1-(1-isobutyl-cyclohexa-2,5-dienyl)-2-((*R*)-*t*-butylsulfinyl)-ethanol **112** (0.421 g, 1.5 mmol) and imidazole (0.21 g, 3.1 mmol) in anhydrous *N*,*N*-dimethylformamide (1.5 cm^3) was added a solution of *t*-butyldimethylsilyl chloride (0.47 g, 3.1 mmol) in *N*,*N*-dimethylformamide (1 cm^3). The solution was stirred for 3 d at room temperature under an inert atmosphere of argon. Then distilled water (30 cm^3) was added and the aqueous layer was extracted with dichloromethane (3×25 cm^3). The combined organic layer was dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude compound was purified by column chromatography (diethyl ether) to give the *title compound* **114** as a white solid (0.144 g, 24%), R_f=0.3 (diethyl ether); mp 80 °C, υ_{max} (neat)/cm^{-1} 2929, 1461, 1256, 1080; δ_H (360 MHz, $CDCl_3$) 0.05 (6H, s, $(CH_3)_2Si$), 0.67 (3H, d, *J* 5.3, CH_3CHCH_2), 0.69 (3H, d, *J* 5.3, CH_3CHCH_2), 0.76 (9H, s, $(CH_3)_3CSi$), 0.98 (1H, dd, *J* 5.2 and 13.6, CH_3CHCH_2), 1.02 (9H, s, $(CH_3)_3CS$), 1.39 (1H, septet, *J* 6.5, CH_3CHCH_3), 1.57 (1H, dd, *J* 6.2 and 12.3, CH_3CHCH_2), 2.17 (1H, dd, *J* 9.4 and 13.1, CH_2S), 2.47 (2H, m, $CHCH_2CH$-CH_2S), 2.59 (1H, dd, *J* 1.0 and 13.1, $CHCH_2CH$), 3.74 (1H, d, *J* 8.6, CHOSi), 5.18 (1H, dd, *J* 2.0 and 10.3, CHCH), 5.44 (1H, dd, *J* 2.1 and 10.5, CHCH), 5.68 (2H, m, 2× CHCH); δ_C (90 MHz, $CDCl_3$) 0.0 (2×q), 18.5 (s), 22.9 (3×q), 24.5 (q), 25.0 (d), 25.2 (q), 26.3 (3×q), 27.0 (t), 46.5 (s), 47.4 (t), 51.8 (t), 52.6 (s), 73.8 (d), 125.8 (d), 125.8 (d), 129.1 (d), 131.5 (d); *m/z* (EI) 400 (M^+, 80%), 341 (100), 285 (60); HR (ESI) 421.2564 (M^+Na $C_{22}H_{42}O_2SSiNa$ requires 421.2566).

Rel-(1*S*,3*R*,3$_a$*R*,7$_a$*R*)-3-(*tert*-butyl-dimethylsilyl)oxy-3$_a$-isopropyl-2,3,3$_a$,6,7,7$_a$-hexahydro-benzo[*b*]thiophene-1-oxide (113a) and _rel_-(1*R*,3*R*,3$_a$*S*,7$_a$*S*)-(*tert*-butyl-dimethylsilyl)oxy-3$_a$-isopropyl-2,3,3$_a$,6,7,7$_a$-hexahydro-benzo[*b*]thiophene-1-oxide (113b)



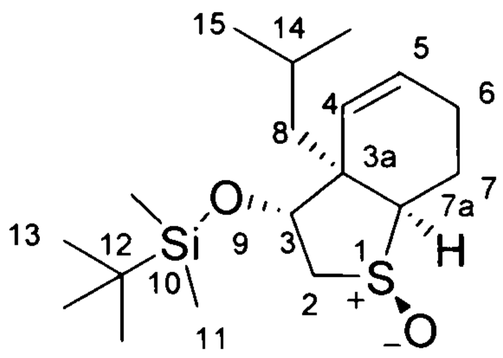
113a



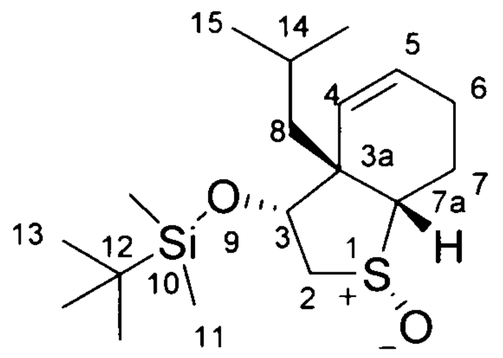
113b

A solution of *rel*-(1*R*)-1-(1-isopropyl-cyclohexa-2,5-dienyl)-1-(*t*-butyl-dimethylsilyl)oxy-2-((*R*)-*t*-butylsulfinyl)-ethane **113** (0.040 g, 0.10 mmol) was placed under an inert atmosphere of argon and refluxed in xylene (0.14 M) for 6.5 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by column chromatography (6:4 diethyl ether/60-80 °C petroleum ether) afforded the *title compounds* **113a** and **113b** as a colourless oil (0.005 g, 15%, dr 4:1), R_f=0.3 (5:5 diethyl ether/60-80 °C petroleum ether); (major diastereoisomer), υ_{max} (neat)/cm^{-1} 2929, 1471, 1257, 1118, 1077, 1057; δ_H (400 MHz, $CDCl_3$) 0.10 (3H, s, 11-H), 0.16 (3H, s, 11-H), 0.92 (15H, s, 13,14-H), 1.97 (2H, m, 6,7-H), 2.10 (1H, septet, *J* 6.6, 8-H), 2.37 (2H, m, 6,7-H), 2.80 (1H, dd, *J* 2.3 and 11.9, 2-H), 3.24 (1H, d, *J* 4.4, 7$_a$-H), 3.54 (1H, dd, *J* 1.6 and 11.5, 2-H), 4.26 (1H, t, *J* 2.2, 3-H), 5.48 (1H, m, 4-H), 6.11 (1H, m, 5-H); δ_C (100 MHz, $CDCl_3$) 18.4 (14-C), 18.7 (7-C), 19.0 (14-C), 22.8 (6-C), 26.0 (13-C), 32.5 (8-C), 57.1 (7$_a$-C), 59.6 (2-C), 77.4 (3-C), 124.9 (5-C), 133.1 (4-C); *m/z* (EI) 328 (M$^+$, 23%), 271 (42), 206 (28), 148 (100); HR (ESI) 351.1776 (M$^+$Na $C_{17}H_{32}O_2SSiNa$ requires 351.1784).

Rel-(1_S_,3_R_,3$_a$_R_,7$_a$_R_)-3-(_tert_-butyl-dimethylsilyl)oxy-3$_a$-isobutyl-2,3,3$_a$,6,7,7$_a$-hexahydro-benzo[_b_]thiophene-1-oxide (114a) and _rel_-(1_R_,3_R_,3$_a$_S_,7$_a$_S_)-(_tert_-butyl-dimethylsilyl)oxy-3$_a$-isobutyl-2,3,3$_a$,6,7,7$_a$-hexahydro-benzo[_b_]thiophene-1-oxide (114b)



114a

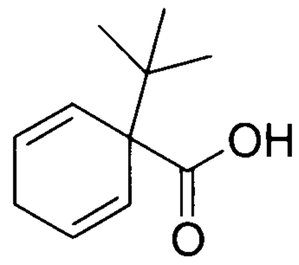


114b

A solution of _rel_-(1_R_)-1-(1-isobutyl-cyclohexa-2,5-dienyl)-1-(_t_-butyl-dimethylsilyl)oxy-2-((_R_)-_t_-butylsulfinyl)-ethane **114** (0.093 g, 0.23 mmol) was placed under an inert atmosphere of argon and refluxed in xylene (0.14 M) for 2.5 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by column chromatography (3:2 diethyl ether/60-80 °C petroleum ether) afforded the *title compounds* **114a** and **114b** as a colourless oil (0.049 g, 62%, dr 4:1), R_f=0.3 (5:5 diethyl ether/60-80 °C petroleum ether); υ_{max} (neat)/cm^{-1} 2954, 1471, 1257, 1160, 1056; (major diastereoisomer) δ_H (400 MHz, $CDCl_3$) 0.03 (3H, s, 11-H), 0.06 (3H, s, 11-H), 0.80 (9H, s, 13-H), 0.82 (3H, s, 15-H), 0.86 (3H, s, 15-H), 1.20 (1H, dd, _J_ 5.7 and 13.9, 8-H), 1.49 (1H, dd, _J_ 6.3 and 13.9, 8-H), 1.63 (1H, m, 14-H), 1.87-2.44 (4H, m, 6,7-H), 2.78 (1H, dd, _J_ 3.9 and 12.6, 2-H), 3.17 (1H, t, _J_ 5.3, 7$_a$-H), 3.36 (1H, dd, _J_ 4.0 and 12.6, 2-H), 4.24 (1H, t, _J_ 3.9, 3-H), 5.46 (1H, d, _J_ 10.4, 4-H), 5.87 (1H, m, 5-H); δ_C (100 MHz, $CDCl_3$) 18.5 (7-C), 23.2 (6-C), 24.9 (15-C), 25.0 (15-C), 26.0 (14-C), 26.1 (13-C), 44.2 (8-C), 51.4 (3$_a$-C), 58.1 (7$_a$-C), 59.3 (2-C), 78.9 (3-C), 130.0 (5-C), 130.1 (4-C); (minor diastereoisomer) identifiable peaks δ_H (400 MHz, $CDCl_3$) 0.00 (6H, s, 11-H), 0.80 (9H, s, 13-H), 0.83 (3H, s, 15-H), 0.85 (3H, s, 15-H), 1.06 (1H, dd, _J_ 4.8 and 14.2, 8-H), 1.49 (1H, dd, _J_ 6.5 and 14.2, 8-H), 2.68 (1H, dd, _J_ 7.8 and 12.6, 2-H), 3.12 (1H, t, _J_ 5.3, 7$_a$-H), 3.52 (1H, dd, _J_ 5.3 and 12.6, 2-H), 3.74 (1H, dd, _J_ 5.3 and 7.8, 3-H), 5.53 (1H, d, _J_ 10.3, 4-H), 5.91 (1H, m, 5-H); δ_C (100 MHz, $CDCl_3$) 47.9 (8-C), 50.8 (3$_a$-C), 58.0 (2-C), 59.3 (7$_a$-C), 76.9 (3-C), 128.4 (5-C), 130.6 (4-C); _m z_

(EI) 343 (M^+, 100%), 285 (25), 148 (63); HR (ESI) 365.1933 (M^+Na $C_{18}H_{34}O_2SSiNa$ requires 365.1940).

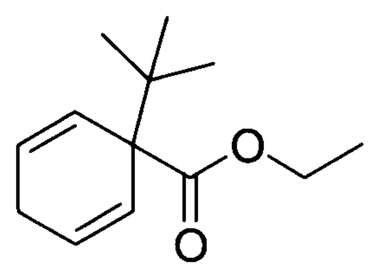
1-*tert*-Butyl-cyclohexa-2,5-diene-1-carboxylic acid (115)[63]



115

Ammonia (300 cm^3) was added to benzoic acid (5.0 g, 40.9 mmol) with careful mechanical stirring. To this, sodium (3.10 g, 135 mmol) was added portionwise until a permanent blue colour persisted, followed by dropwise addition of 2-iodo-2-methylpropane (16 cm^3, 135 mmol). The reaction mixture was left for 1 h, whilst the ammonia evaporated, and ice was added to the remaining solid, followed by dilute H_2SO_4. The product was extracted with diethyl ether (3×80 cm^3) and the combined ethereal extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The crude compound was purified by column chromatography (1:4 diethyl ether/60-80 °C petroleum ether) to afford the title compound **115** as a white solid (1.37 g, 23%). R_f=0.2 (1:4 diethyl ether/60-80°C petroleum ether); δ_H (360 MHz, $CDCl_3$) 0.98 (9H, s, 3×C*H*$_3$), 2.59 (2H, m, CHC*H*$_2$CH), 5.91-6.05 (4H, m, 2×C*H*C*H*), 11.0 (1H, bs, COO*H*).

1-*tert*-Butyl-cyclohexa-2,5-dienecarboxylic acid ethyl ester (116)



116

Method A.

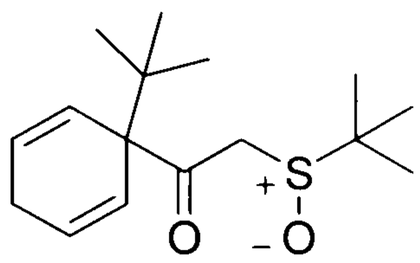
Potassium carbonate (2.5 g, 18.3 mmol) and iodoethane (2.3 cm^3, 29.2 mmol) were added to a solution of 1-*tert*-butylcyclohexa-2,5-diene-1-carboxylic acid **115** (1.324 g, 7.30 mmol) in acetone (21 cm^3) and distilled water (1.1 cm^3), and the mixture was heated to 75 °C. After 3 h, the reaction was cooled to room temperature, diluted with water (50 cm^3) and 10% HCl (2.8 cm^3), extracted with dichloromethane (3×50 cm^3), washed with saturated NaCl (100 cm^3), dried over $MgSO_4$ and evaporated *in vacuo* to afford the *title compound* **116** as a colourless oil (1.432 g, 94%), R_f=0.3 (2:8 diethyl ether/60-80 °C petroleum ether); υ_{max} (neat)/cm^{-1} 2969, 1724, 1365; δ_H (360 MHz, $CDCl_3$) 0.95 (9H, s, $C(CH_3)_3$), 1.28 (3H, t, *J* 7.1, CH_3CH_2), 2.57 (2H, d, *J* 2.5, $CHCH_2CH$), 4.15 (2H, q, *J* 7.2, CH_3CH_2), 5.87-5.95 (2H, m, 2×CHC*H*), 6.04-6.08 (2H, m, 2×CHC*H*); δ_C (90 MHz, $CDCl_3$) 14.6 (q), 26.4 (3×q), 26.6 (t), 39.0 (s), 53.2 (s), 60.8 (t), 126.0 (2×d), 126.6 (2×d), 174.3 (s); *m/z* (EI) 209 (M^+H, 3%), 155 (100), 123 (62), 105 (47), 79 (54); HR (ESI) 208.1458 (M^+ $C_{13}H_{20}O_2$ requires 208.1402).

Method B.

An oven dried three-necked round bottomed flask was placed under an inert atmosphere of argon. To the flask was added ethyl benzoate (3.80 cm^3, 26 mmol) dissolved in dry THF (8 cm^3) and *t*-BuOH (2.4 cm^3, 26 mmol). The reaction was cooled to -78 °C and ammonia was added (80 cm^3). Small pieces of sodium (1.98 g, 86.4 mmol) were added until the deep blue colourisation persisted for 30 min. Excess metal was quenched with piperylene (3 cm^3, 30 mmol) to give a dark orange solution. 2-Iodo-2-methylpropane (10.2 cm^3, 86.4 mmol) was then added. The reaction was allowed to warm to room temperature, and the ammonia to evaporate under an over pressure of argon overnight

before being quenched with NH_4Cl (2 g). The thick mixture was diluted with distilled water (30 cm^3) and diethyl ether (30 cm^3), the phases were separated and the aqueous layer was extracted with diethyl ether (3×30 cm^3). The combined organic phases were washed with saturated $NaHCO_3$ (30 cm^3), saturated NaCl (50 cm^3), dried over $MgSO_4$ and evaporated *in vacuo* to afford the title compound **116** (5.011 g, 93%) as a colourless oil, *data as above*.

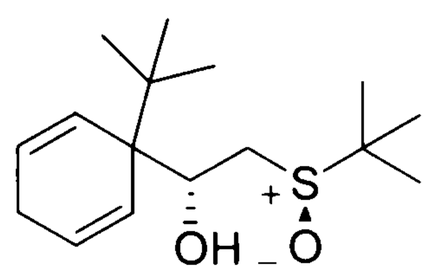
1-(1-*tert*-Butyl-cyclohexa-2,5-dienyl)-2-(*t*-butylsulfinyl)-ethanone (117)



117

To a solution of lithium diisopropylamide (43.5 mmol) in dry THF (46 cm^3) at -78 °C was added dropwise a solution of *t*-butyl methyl sulfoxide **75** (4.50 g, 37.7 mmol) in THF (7 cm^3). The reaction was stirred for 2 h. 1-*tert*-Butyl-cyclohexa-2,5-dienecarboxylic acid ethyl ester **116** (3.928 g, 18.9 mmol) was then added and the reaction was stirred at -78 °C for a further 3 h. The reaction was then allowed to warm to room temperature, quenched with saturated NH_4Cl (50 cm^3) and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3×50 cm^3) and the combined organic extracts were washed with saturated NaCl (50 cm^3), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (diethyl ether) to afford the *title compound* **117** as a white solid (3.880 g, 73%), R_f=0.3 (diethyl ether); mp 80 °C, υ_{max} (neat)/cm^{-1} 2962, 1680, 1042; δ_H (360 MHz, $CDCl_3$) 1.01 (9H, s, $C(CH_3)_3$), 1.24 (9H, s, $(CH_3)_3CS$), 2.70-2.72 (2H, m, $CHCH_2CH$), 3.68 (2H, dd, *J* 15.0 and 18.6, CH_2S), 5.86-5.93 (2H, m, 2×C*H*CH), 6.02-6.09 (2H, m, 2×C*H*CH); δ_C (90 MHz, $CDCl_3$) 23.2 (3×q), 26.6 (3×q), 26.7 (t), 38.8 (s), 54.2 (s), 58.7 (t), 59.8 (s), 125.8 (d), 126.0 (d), 128.7 (d), 128.8 (d), 204.3 (s); *m/z* (EI) 283 (M^+H, 3%), 168 (100), 123 (40), 57 (53).

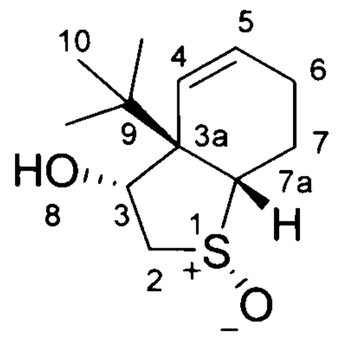
Rel-(1*R*)-1-(1-*tert*-butyl-cyclohexa-2,5-dienyl)-2-((*R*)-*t*-butylsulfinyl)-ethanol (118)



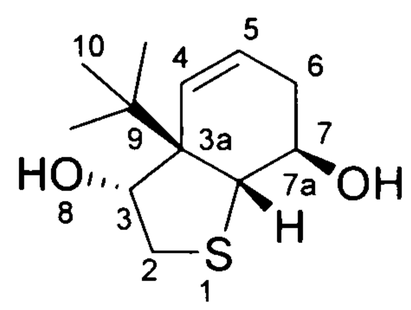
118

To a solution of 1-(1-*tert*-butyl-cyclohexa-2,5-dienyl)-2-(*t*-butylsulfinyl)-ethanone **117** (1.059 g, 3.75 mmol) in dry THF (37 cm^3) at –78 °C was added dropwise a 1M solution of diisobutylaluminum hydride in toluene (4.1 cm^3, 4.07 mmol). After 1 h at –78 °C, methanol (37 cm^3) was added to the reaction vessel. The solvent was then evaporated *in vacuo* and the residue diluted with distilled water (40 cm^3) and extracted with dichloromethane (3×40 cm^3). The organic layer was then washed with a 5% NaOH solution (50 cm^3), dried over $MgSO_4$ and evaporated *in vacuo* to afford the *title compound* **118** as a white solid (0.938 g, 89%), R_f=0.1 (diethyl ether); mp 148 °C, υ_{max} (neat)/cm^{-1} 3435, 2957, 1087, 1030; δ_H (360 MHz, $CDCl_3$) 1.03 (9H, s, C(C*H*$_3$)$_3$), 1.25 (9H, s, (C*H*$_3$)$_3$CS), 2.50-2.71 (4H, m, CHC*H*$_2$CH, C*H*$_2$S), 3.59 (1H, d, *J* 5.5, OH), 4.43-4.48 (1H, m, C*H*OH), 5.47 (1H, m, C*H*CH), 5.81-5.86 (1H, m, C*H*CH), 5.99 (2H, s, 2×C*H*CH); δ_C (90 MHz, $CDCl_3$) 23.4 (3×q), 27.4 (t), 27.6 (3×q), 38.6 (s), 48.8 (s), 51.8 (t), 53.0 (s), 69.2 (d), 126.1 (d), 126.8 (d), 127.0 (d), 129.7 (d); *m/z* (EI) 285 (M^+H, 7%), 156 (10), 149 (43), 105 (100), 57 (74); HR (ESI) 307.1717 (M^+Na $C_{16}H_{28}O_2SNa$ requires 307.1702).

Rel-(1_R_,3_R_,3$_a$_S_,7$_a$_S_)-3$_a$-_tert_-butyl-1-oxo-2,3,3$_a$,6,7,7$_a$-hexahydro-1_H_-1λ^4-benzo[_b_]thiophen-3-ol (118a) and _rel_-(3_R_,3$_a$_S_,7_R_,7$_a$_R_)-_tert_-butyl-2,3,3a,6,7,7a-hexahydro-benzo[_b_]thiophene-3,7-diol (118b)



118a

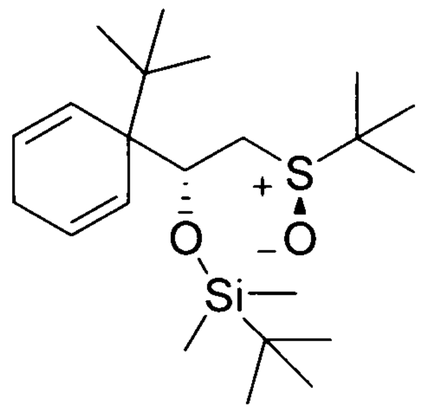


118b

A solution of *rel*-(1*R*)-1-(1-*tert*-butyl-cyclohexa-2,5-dienyl)-1-(*t*-butyl-dimethylsilyl)oxy-2-((*R*)-*t*-butylsulfinyl)-ethane **118** (0.168 g, 0.59 mmol) was placed under an inert atmosphere of argon and refluxed in xylene (0.14 M) for 4 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by column chromatography (diethyl ether) afforded the *title compound* **118b** as a colourless oil (0.003 g, 2%) followed by the starting material **118** (0.027 g, 16%) and by the *title compound* **118a** as a colourless oil (0.055 g, 41%); **118b** R_f=0.3 (95:5 diethyl ether/methanol); υ_{max} (neat)/cm^{-1} 3326, 2952, 1196, 1056; δ_H (400 MHz, $CDCl_3$) 1.03 (9H, s, 10-H), 1.53 (1H, bs, OH), 1.69-1.94 (1H, m, 6-H), 2.28-2.36 (1H, m, 6-H), 2.50 (1H, bs, OH), 2.78 (1H, dd, *J* 5.9 and 11.8, 2-H), 3.00-3.05 (2H, m, 7$_a$,2-H), 3.62-3.67 (1H, m, 7-H), 4.39-4.44 (1H, m, 3-H), 5.67 (1H, dd, *J* 7.3 and 24.2, 4-H), 5.92-5.98 (1H, m, 5-H); δ_C (100 MHz, $CDCl_3$) 26.7 (10-C), 30.9 (6-C), 37.9 (2-C), 56.4 (7$_a$-C), 60.7 (3$_a$-C), 72.0 (7-C), 78.2 (3-C), 128.2 (5-C), 128.6 (4-C); *m/z* (EI) 228 (M^+, 16%), 156 (100), 95 (77), 57 (97); HR (ESI) 251.1061 (M^+Na $C_{12}H_{20}O_2SNa$ requires 251.1076); **118a** R_f=0.1 (95:5 diethyl ether/methanol); υ_{max} (neat)/cm^{-1} 3199, 2951, 1361, 1000; δ_H (360 MHz, $CDCl_3$) 0.98 (9H, s, 10-H), 1.98-2.21 (2H, m, 6,7-H), 2.53-2.60 (2H, m, 6,7-H), 2.68 (1H, dd, *J* 4.7 and 14.0, 2-H), 2.90 (1H, d, *J* 7.2, 7$_a$-H), 3.35 (1H, d, *J* 1.1 and 14.0, 2-H), 3.83 (1H, d, *J* 11.5, OH), 4.65-4.69 (1H, m, 3-H), 5.90 (1H, d, *J* 10.9, 4-H), 6.11-6.15 (1H, m, 5-H); δ_C (100 MHz, $CDCl_3$) 18.8 (6-C), 21.6 (7-C), 26.9 (10-C), 37.5 (9-C), 53.4 (3$_a$-C), 54.3 (2-C), 60.7 (7$_a$-C), 81.2 (3-C), 127.2 (5-C),

130.9 (4-C); *m/z* (EI) 228 (M^+, 7%), 136 (100), 121 (57), 57 (64): HR (ESI) 251.1077 (M^+Na $C_{12}H_{20}O_2SNa$ requires 251.1076).

Rel-(1_R_)-1-(1-_tert_-butyl-cyclohexa-2,5-dienyl)-1-(_t_-butyl-dimethylsilyl)oxy-2-((_R_)-_t_-butylsulfinyl)-ethane (119)

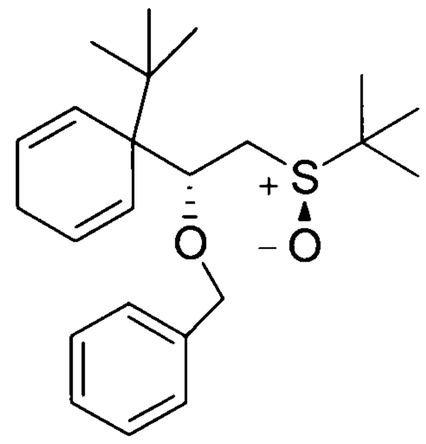


119

To a stirred solution of *rel*-(1*R*)-1-(1-*tert*-butyl-cyclohexa-2,5-dienyl)-2-((*R*)-*t*-butylsulfinyl)-ethanol **118** (0.310 g, 1.09 mmol) in dichloromethane (2 cm^3) was added 2,6-lutidine (0.19 cm^3, 1.64 mmol) and *t*-butyldimethylsilyl trifluoromethane sulfonate (0.3 cm^3, 1.31 mmol) at -78 °C. The solution was allowed to warm to room temperature and stirred for 3 d. Then saturated $NaHCO_3$ (5 cm^3) was added and the reaction mixture was poured into dichloromethane (10 cm^3) and diluted with distilled water (5 cm^3). The layers were separated and the aqueous phase was extracted with dichloromethane (3×10 cm^3). The combined organic layer was dried over $MgSO_4$, filtered and the solvent evaporated *in vacuo*. The crude compound was purified by column chromatography (7:3 diethyl ether/60-80 °C petroleum ether) to afford the *title compound* **119** as a colourless oil (0.144 g, 32%), R_f=0.3 (diethyl ether); υ_{max} (neat)/cm^{-1} 2929, 1472, 1258, 1083, 1052; δ_H (360 MHz, $CDCl_3$) 0.21 (3H, s, $(CH_3)_2Si$), 0.22 (3H, s, $(CH_3)_2Si$), 0.90 (9H, s, $(CH_3)_3CSi$), 0.99 (9H, s, $(CH_3)_3C$), 1.18 (9H, s, $(CH_3)_3CS$), 2.22 (1H, q, *J* 7.1, $CHCH_2CH$), 2.59 (2H, d, *J* 2.2, CH_2S, $CHCH_2CH$), 3.09 (1H, dd, *J* 1.5 and 13.6, CH_2S), 4.48 (1H, dd, *J* 1.4 and 7.1, CHOSi), 5.51 (1H, dd, *J* 2.0 and 10.4, CHCH), 5.79 (1H, m, CHCH), 5.81-5.90 (2H, m, 2×CHCH); δ_C (90 MHz, $CDCl_3$) 0.0 (2×q), 18.5 (s), 23.0 (3×q), 26.4 (3×q), 27.0 (t), 27.5 (3×q), 37.8 (s), 49.9 (s), 52.5 (t), 53.2 (s), 70.9 (d), 125.2

(d), 126.0 (d), 127.3 (d), 130.7 (d); *m/z* (EI) 413 (M^+, 7%), 337 (88), 207 (46), 57 (100): HR (ESI) 421.2588 (M^+Na $C_{22}H_{42}O_2SSiNa$ requires 421.2567).

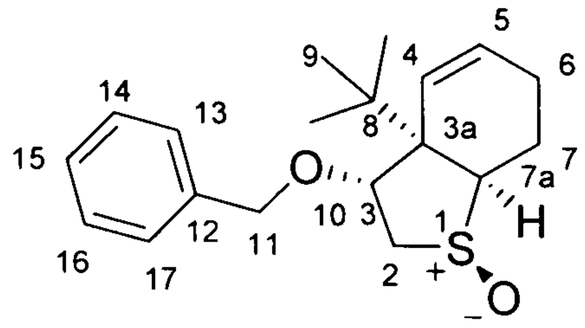
Rel-(1_R_)-1-(1-_tert_-butyl-cyclohexa-2,5-dienyl)-1-benzyloxy-2-((_R_)-_t_-butylsulfinyl)-ethane (120)



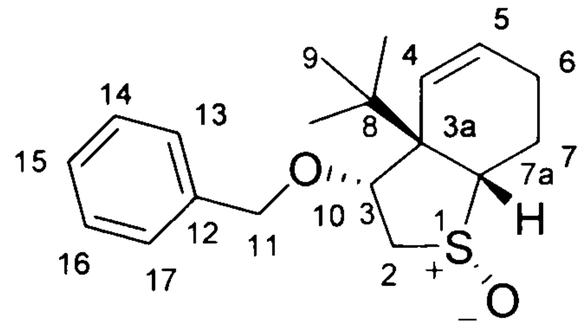
120

To a stirred suspension of sodium hydride (0.58 mmol) in dry THF (3 cm^3) at 0 °C was added dropwise a solution of *rel*-(1*R*)-1-(1-*tert*-butyl-cyclohexa-2,5-dienyl)-2-((*R*)-*t*-butylsulfinyl)-ethanol **118** (0.118 g, 0.42 mmol) in THF (1 cm^3). Benzyl bromide (0.046 cm^3, 0.42 mmol) was added after 2 h at 0 °C. The reaction was then allowed to warm to room temperature overnight. The reaction was quenched with distilled water (20 cm^3) and the aqueous layers extracted with diethyl ether (3×25 cm^3). The combined organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by column chromatography (diethyl ether) to afford the *title compound* **120** as a white solid (0.112 g, 71%), R_f=0.3 (diethyl ether); mp 96 °C; υ_{max} (neat)/cm^{-1} 1463, 1035; δ_H (360 MHz, $CDCl_3$) 0.95 (9H, s, $(CH_3)_3CS$), 1.12 (9H, s, $(CH_3)_3C$), 2.53-2.59 (3H, m, $CHCH_2CH$, CH_2S), 2.85 (1H, dd, *J* 13.3 and 1.8, CH_2S), 4.19 (1H, dd, *J* 1.8 and 9.0, $CHOCH_2$), 4.71 (1H, d, *J* 11.2, CH_2OCH), 4.94 (1H, d, *J* 11.2, CH_2OCH), 5.43 (1H, dd, *J* 2.1 and 10.4, $CHCH$), 5.82-5.85 (1H, m, $CHCH$), 5.95-5.98 (2H, m, 2×$CHCH$), 7.27-7.39 (5H, m, 5×Ar-*H*); δ_C (90 MHz, $CDCl_3$) 23.2 (3×q), 27.4 (t), 27.7 (3×q), 38.7 (s), 50.0 (s), 52.6 (t), 53.5 (s), 76.3 (t), 77.3 (d), 125.7 (d), 126.4 (d), 126.9 (d), 127.4 (d), 127.5 (2×d), 128.2 (2×d), 129.9 (d), 138.5 (s); *m/z* (EI) 375 (M^+, 27%), 153 (23), 91 (98), 57 (100): HR (ESI) 397.2165 (M^+Na $C_{23}H_{34}O_2SNa$ requires 397.2171).

Rel-(1*S*,3*R*,3$_a$*R*,7$_a$*R*)-3-benzyloxy-3a-*tert*-butyl-2,3,3a,6,7,7a-hexahydro-benzo[*b*]thiophene 1-oxide (120a) or *rel*-(1*R*,3*R*,3$_a$*S*,7$_a$*S*)-3-benzyloxy-3a-*tert*-butyl-2,3,3a,6,7,7a-hexahydro-benzo[*b*]thiophene 1-oxide (120b)



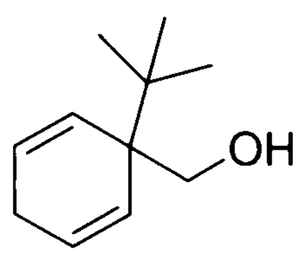
or



120a **120b**

A solution of *rel*-(1*R*)-1-(1-*tert*-butyl-cyclohexa-2,5-dienyl)-1-benzyloxy-2-((*R*)-*t*-butylsulfinyl)-ethane **120** (0.111 g, 0.30 mmol) was placed under an inert atmosphere of argon and refluxed in xylene (0.14 M) for 1 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by column chromatography (diethyl ether) afforded the starting material (0.07 g, 62%) followed by the *title compound* **120a** or **120b** as a colourless oil (0.008 g, 8%), R_f=0.2 (diethyl ether); υ_{max} (neat)/cm^{-1} 1657, 1454, 1099, 1047; δ_H (360 MHz, $CDCl_3$) 0.89 (9H, s, 9-H), 1.89-2.00 (1H, m, 7-H), 2.04-2.05 (1H, m, 6-H), 2.12-2.17 (1H, m, 7-H), 2.29-2.31 (1H, m, 6-H), 2.86 (1H, t, *J* 11.2, 2-H), 3.37 (1H, t, *J* 5.7, 7$_a$-H), 3.59 (1H, dd, *J* 5.0 and 11.2, 2-H), 3.92 (1H, dd, *J* 5.0 and 11.2, 3-H), 4.47 (1H, d, *J* 11.7, 11-H), 4.51 (1H, d, *J* 11.7, 11-H), 5.96 (1H, d, *J* 10.7, 4-H), 6.15-6.20 (1H, m, 5-H), 7.25 (5H, m, 13-17-H); δ_C (90 MHz, $CDCl_3$) 19.4 (t), 22.5 (t), 27.4 (3×q), 37.2 (s), 52.9 (t), 53.5 (s), 55.8 (d), 77.2 (t), 126.0 (d), 127.7 (2×d), 127.9 (d), 128.5 (2×d), 130.6 (d) 137.9 (s); *m/z* (EI) 318 (M$^+$, 14%), 153 (31), 91 (100); HR (ESI) 341.1541 (M$^+$Na $C_{19}H_{26}O_2SNa$ requires 341.1545).

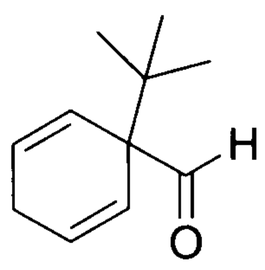
(1-*tert*-Butyl-cyclohexa-2,5-dienyl)-methanol (131)



131

To a solution of 1-*tert*-butyl-cyclohexa-2,5-dienecarboxylic acid ethyl ester **116** (2.065 g, 9.9 mmol) in dry diethyl ether (20 cm^3) at 0 °C was added a solution of lithium aluminum hydride (0.56 g, 14.9 mmol) in dry diethyl ether (15 cm^3). After 30 min at 0 °C, the reaction was quenched with distilled water (0.25 cm^3), 15% NaOH (0.40 cm^3) and water (0.55 cm^3) again. The mixture was filtered through Celite, dried over $MgSO_4$, and filtered. The solvent was removed *in vacuo* to afford the *title compound* **131** as a white solid (1.302 g, 79%), R_f=0.3 (4:6 diethyl ether/60-80 °C petroleum ether); υ_{max} (neat)/cm^{-1} 3292, 1464, 1203; δ_H (360 MHz, $CDCl_3$) 0.82 (9H, s, $(CH_3)_3C$), 1.11 (1H, bs, OH), 2.56 (2H, m, $CHCH_2CH$), 3.47 (2H, d, *J* 4.7, CH_2OH), 5.55 (2H, m, 2×CHC*H*), 5.98 (2H, m, 2×CHC*H*); δ_C (90 MHz, $CDCl_3$) 26.3 (3×q), 27.0 (t), 36.7 (s), 48.5 (s), 65.9 (t), 128.5 (2×d), 129.1 (2×d); *m/z* (ESI) 184 (M^+NH_3; 100%), 139 (27), 122 (12).

1-*tert*-Butyl-cyclohexa-2,5-dienecarbaldehyde (130)

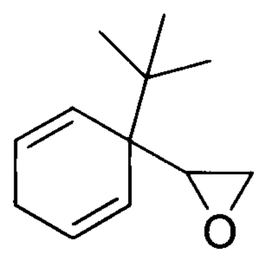


130

To a flask fitted with a low temperature thermometer was added dichloromethane (60 cm^3) and *N*-chlorosuccinimide (1.55 g, 11.6 mmol). The slighly turbid solution was cooled to 0 °C and treated with methyl sulfide (1.1 cm^3, 15.4 mmol) which resulted in the formation of a flocculent white precipitate. The mixture was cooled to -25 °C and a solution of (1-*tert*-butyl-cyclohexa-2,5-dienyl)-methanol **131** (1.284 g, 7.7 mmol) in

dichloromethane (4.5 cm^3) was slowly added to maintain the temperature below -22 °C. The mixture was stirred at -25 °C for an additional 2 h and then triethylamine (1.9 cm^3, 13.9 mmol) was added. The mixture was poured into distilled water (30 cm^3) and extracted with dichloromethane (3×30 cm^3). The combined organic layer was dried over $MgSO_4$, filtered and the solvent evaporated *in vacuo* to afford the crude aldehyde **130** as a yellow oil (1.791 g) R_f=0.3 (4:6 diethyl ether/60-80 °C petroleum ether).

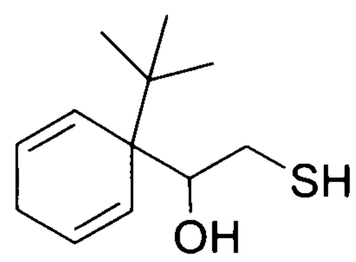
2-(1-*tert*-Butyl-cyclohexa-2,5-dienyl)-oxirane (129)



129

To a stirred solution of trimethylsulfoxonium iodide (2.8 g, 12.8 mmol) in dry methyl sulfoxide (13 cm^3), placed under nitrogen, was added sodium hydride (12.8 mmol). After stirring for 30 min, a solution of 1-*tert*-butyl-cyclohexa-2,5-dienecarbaldehyde **130** (1.746 g, 10.6 mmol) in dry methyl sulfoxide (6 cm^3) was added and the reaction mixture stirred at room temperature for 2 h. After cooling and addition of distilled water (50 cm^3), the mixture was extracted with diethyl ether (3×50 cm^3). The combined extracts were washed with saturated NaCl (50 cm^3), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude compound was purified by column chromatography (5% Et_3N in diethyl ether) to afford the *title compound* **129** as a colourless oil (0.965 g, 51%), R_f=0.3 (diethyl ether), υ_{max} (neat)/cm^{-1} 1476, 1074; δ_H (360 MHz, $CDCl_3$) 1.00 (9H, s, $(CH_3)_3C$), 2.44 (1H, dd, *J* 2.8 and 5.1, CH_2OCH), 2.59 (3H, m, $CHCH_2CH.CH_2OCH$), 3.12 (1H, dd, *J* 2.9 and 4.0, CH_2OCH), 5.59 (2H, m, 2×CHCH), 5.90 (2H, m, 2×CHCH); δ_C (90 MHz, $CDCl_3$) 26.3 (3×q), 27.1 (t), 38.3 (s), 43.9 (t), 45.0 (s), 54.9 (d), 125.7 (d), 126.6 (d), 126.7 (d), 127.5 (d); *m/z* (EI) 179 (M^+, 42%), 161 (100), 108 (10); HR (ESI) 200.1073 (M^+Na $C_{12}H_{17}OSNa$ requires 200.1172).

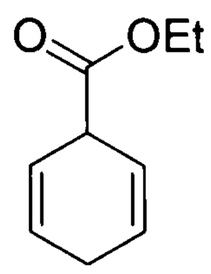
1-(1-*tert*-Butyl-cyclohexa-2,5-dienyl)-2-mercapto-ethanol (127)



127

A solution of 2-(1-*tert*-butyl-cyclohexa-2,5-dienyl)-oxirane **129** (0.517 g, 2.9 mmol) and carbon disulfide (0.16 cm^3) was added slowly to a solution of sodium hydrosulfide (0.2 g, 3.5 mmol) and methanol (2 cm^3). After 4.5 h, the pH of the mixture was adjusted to ~1 by adding concentrated HCl. Distilled water (10 cm^3) was added to dissolve NaCl and the mixture was extracted with diethyl ether (3×20 cm^3). The combined ether extracts were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude compound was purified by column chromatography (5:95 diethyl ether/60-80 °C petroleum ether) to afford the *title compound* **127** as a colourless oil (0.14 g, 23%), R_f= 0.3 (5:95 diethyl ether/60-80 °C petroleum ether), υ_{max} (neat)/cm^{-1} 3400, 1706, 1364, 1057; δ_H (360 MHz, $CDCl_3$) 1.01 (9H, s, $(CH_3)_3C$), 1.26 (1H, dd, *J* 7.6 and 10.2, SH), 2.36 (1H, m, CH_2SH), 2.57 (1H, d, *J* 3.2, OH), 2.80 (2H, m, $CHCH_2CH$), 3.60-3.64 (1H, m, CH_2SH), 3.62 (1H, dt, *J* 2.8 and 10.6, CHOH), 5.43 (1H, m, CHCH), 5.86 (1H, m, 2×CHCH), 5.95 (1H, m, CHCH); δ_C (90 MHz, $CDCl_3$) 27.4 (3×q), 31.8 (t), 38.4 (s), 48.7 (s), 75.6 (t), 75.7 (d), 126.3 (d), 126.3 (d), 126.9 (d), 129.1 (d); *m/z* (EI) 213 (M^+, 7%), 195 (15), 150 (6); HR (ESI) 235.1573 (M^+Na $C_{12}H_{20}OSNa$ requires 235.1129).

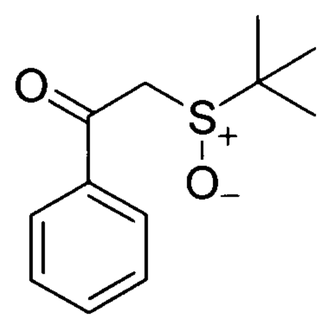
Cyclohexa-2,5-dienecarboxylic acid ethyl ester (132)[68]



132

Ethyl benzoate (7.0 g, 47 mmol) along with distilled water (1.24 cm^3, 69 mmol) was dissolved in dry THF (75 cm^3) and condensed ammonia (150 cm^3), under argon atmosphere, at – 78 °C. Sodium (2.68 g, 116 mmol) was then added in pieces and the reaction was stirred for 40 min. The mixture was then poured into a large excess of NH_4Cl solution. After extraction with diethyl ether (3×40 cm^3), the organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford the title compound **132** (5.51 g, 79%); δ_H (360 MHz, $CDCl_3$) 1.28 (3H, t), 2.68 (2H, m), 3.73 (1H, m), 4.18 (2H, q), 5.87 (4H, m).

2-(2-Methyl-propane-2-sulfinyl)-1-phenyl-ethanone (133)

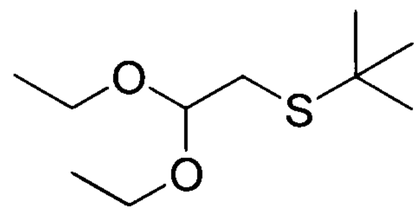


133

To a solution of lithium diisopropylamide (8.34 mmol) in dry THF (20 cm^3) at -78 °C was added dropwise a solution of *t*-butyl methyl sulfoxide **75** (0.5 g, 4.17 mmol) in THF (2 cm^3). The reaction was stirred for 2 h. 1-*tert*-Butyl-cyclohexa-2,5-dienecarboxylic acid ethyl ester **132** (3.928 g, 18.9 mmol) was then added at -78 °C and the reaction was then left to warm to room temperature and was then refluxed for a further 2 h. The reaction was then allowed to cool to room temperature, quenched with saturated NH_4Cl (20 cm^3) and the organic layer was separated. The aqueous layer was extracted with diethyl ether

(3×20 cm^3) and the combined organic extracts were washed with saturated NaCl (20 cm^3), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (diethyl ether) to afford the title compound **133** as a colourless oil (0.145 g, 15%), R_f=0.2 (diethyl ether); analytical data agree with literature values: $^{115}\delta_H$ (360 MHz, $CDCl_3$) 1.35 (9H, s), 3.98 (1H, d), 4.18 (1H, d), 7.58 (4H, m), 8.05 (1H, m).

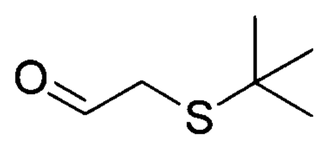
2-*tert*-Butylthioacetaldehyde diethylacetal (137)[69]



137

To a suspension of NaH (22 mmol) in dry THF (15 cm^3) at 0 °C under inert atmosphere, was slowly added *t*-butyl thiol (2.50 cm^3, 22 mmol), resulting in the evolution of hydrogen and the formation of a colourless precipitate. This suspension was stirred for 45 min, then 2-bromoacetaldehyde diethyl acetal (3.44 cm^3, 22 mmol) was slowly added. The resultant mixture was heated for 3 h and then stirred overnight at room temperature. The reaction mixture was quenched with a solution of saturated NaCl (40 cm^3) and extracted with diethyl ether (3×50 cm^3). The combined ethereal extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound **137** as a colourless liquid (4.42 g, 97%); δ_H (360 MHz, $CDCl_3$) 1.22 (6H, t), 1.33 (9H, s), 2.75 (2H, d), 3.61 (4H, m), 4.65 (1H, t); δ_C (90 MHz, $CDCl_3$) 15.6 (q), 31.3 (3×q), 32.4 (t), 42.4 (s), 62.0 (t), 102.8 (t).

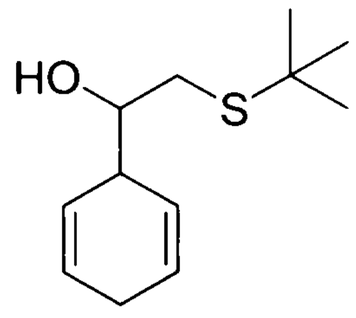
tert-Butylsulfanyl-acetaldehyde (136)[69]



136

To a solution of 2-*tert*-butylthioacetaldehyde diethylacetal **137** (2.63 g, 12.7 mmol) in cyclohexane (98 cm^3) was added 6N hydrochloric acid (45 cm^3). The mixture was heated at reflux for 2 h. After cooling to room temperature, a pH-7 buffer solution (50 cm^3) was added. After separation of the two layers, the organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound **136** as a colourless liquid (0.92 g, 55%); δ_H (360 MHz, $CDCl_3$) 1.33 (9H, s), 3.27 (2H, d), 9.56 (1H, t); δ_C (90 MHz, $CDCl_3$) 31.4 (3×q), 40.2 (t), 43.8 (s), 197.9 (s).

2-*tert*-Butylsulfanyl-1-cyclohexa-2,5-dienyl-ethanol (134)



134

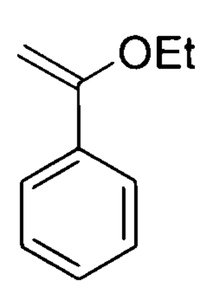
To a cooled (-78 °C) solution of 1,4-cyclohexadiene **135** (5.9 cm^3, 62.7 mmol) in dry THF (100 cm^3) were added *s*-butyllithium (1.4 M in cyclohexane, 45 cm^3, 62.7 mmol), and dry *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (9.5 cm^3, 62.7 mmol). The yellow solution was warmed to –45 °C, and after 2.5 h was treated with *tert*-butylsulfanyl-acetaldehyde **136** (1.1 g, 8.36 mmol) in THF (10 cm^3). After 10 min at –45 °C, the solution was warmed to 23 °C and treated with saturated aqueous NH_4Cl solution (500 cm^3). The organic phase was diluted with diethyl ether (500 cm^3), separated from the aqueous phase, washed with saturated NaCl solution (300 cm^3), dried over Na_2SO_4 and concentrated *in vacuo*. The crude compound was purified by column chromatography

(4:6 diethyl ether/60-80 °C petroleum ether) to afford the *title compound* **134** as a yellow oil (0.48 g, 27%), R_f=0.2 (4:6 diethyl ether/60-80 °C petroleum ether); δ_H (360 MHz, $CDCl_3$) 1.33 (9H, s), 2.49-2.86 (4H, m), 3.66 (1H, m), 5.68-5.97 (4H, m); *m/z* (EI) 212 (M^+, 3%), 133 (17), 104 (37), 79 (29), 57 (100).

Dicyclopentadienyldimethyltitanium[71]

A solution of methyllithium (0.9 M, 33.8 mmol) in diethyl ether (40 cm^3) was added dropwise to a suspension of dicyclopentadienyltitaniumdichloride (4.017 g, 16.1 mmol) in diethyl ether (8 cm^3) cooled in an ice bath. After 1 hour, the reaction mixture was quenched with ice-water, the organic layer separated, dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford the title compound (3.013 g, 90%). The resulting bright orange crystals were dissolved in THF (30 cm^3) and stored in the dark, in the refrigerator.

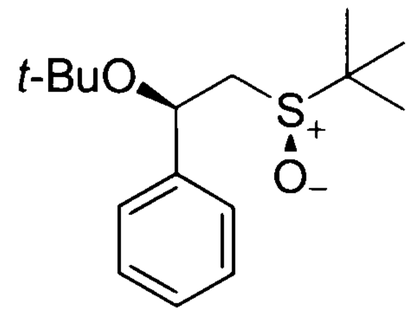
(1-Ethoxy-vinyl)-benzene (138)



138

A solution of dicyclopentadienyldimethyltitanium in dry THF (0.5 M, 1.5 mmol) was mixed with ethyl benzoate (0.11 g, 0.75 mmol) and stirred under inert atmosphere and in the dark at 65 °C. After 2.5 hours, the mixture was diluted with 60-80 °C petroleum ether (5 cm^3). The yellow-orange precipitate was removed by filtration, and the filtrate was concentrated *in vacuo* to afford a mixture of ethyl benzoate and of *title compound* **138** as an orange oil (0.238 g); identifiable peaks δ_H (360 MHz, $CDCl_3$) 3.93 (2H, q, *J* 7.0), 4.20 (1H, d, *J* 2.6), 4.63 (1H, d, *J* 2.6).

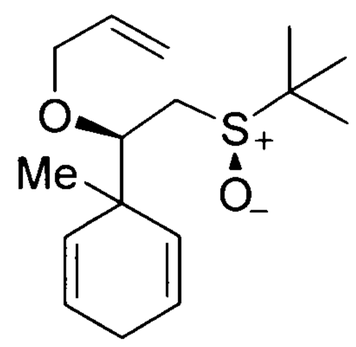
Rel-(1_R_)-[1-_tert_-Butoxy-2-((_R_)-2-methyl-propane-2-sulfinyl)-ethyl]-benzene (145)



145

A solution of *rel*-(1*R*)-1-(1-*tert*-butyl-cyclohexa-2,5-dienyl)-1-(*t*-butyl-dimethylsilyl)oxy-2-((*R*)-*t*-butylsulfinyl)-ethane **118** (0.168 g, 0.59 mmol) was placed under an inert atmosphere of argon and refluxed in xylene (0.14 M) for 4 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by column chromatography (diethyl ether) afforded the *title compound* **145** as a colourless oil (0.042 g, 9%) followed by the starting material **118** (0.007 g, 2%); **145** R_f=0.2 (diethyl ether); δ_H (360 MHz, $CDCl_3$) 1.03 (9H, s, $(CH_3)_3C$), 1.15 (9H, s, $(CH_3)_3C$), 1.88 (1H, dd, *J* 5.1 and 13.1, CH_2S), 2.33 (1H, dd, *J* 10.1 and 12.1, CH_2S), 3.87-3.94 (1H, m, OC*H*), 5.50 (1H, t, *J* 9.3, Ar-H), 6.18-6.23 (2H, m, Ar-H), 6.46-6.48 (2H, m, Ar-H); δ_C (90 MHz, $CDCl_3$) 23.2 (q), 30.8 (q), 33.9 (d), 37.1 (s), 43.7 (t), 53.2 (s), 118.7 (d), 123.8 (d), 126.6 (d), 129.0 (d), 130.0 (d)147.8 (s).

Rel-(1_R_)-3-[1-allyloxy-2-((_R_)-2-methyl-propane-2-sulfinyl)-ethyl]-3-methyl-cyclohexa-1,4-diene (166)

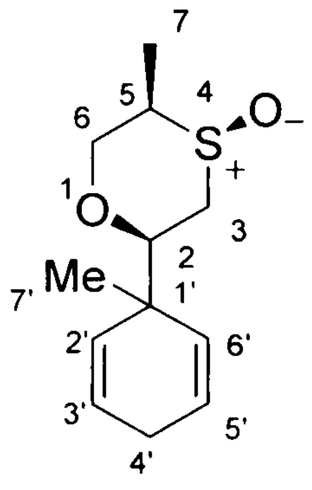


166

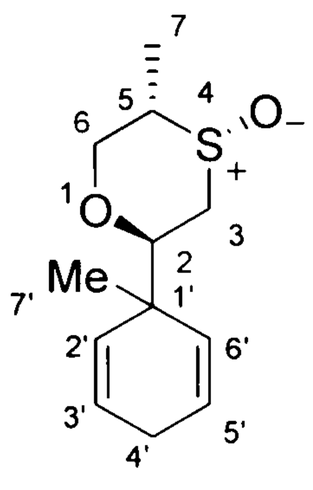
To a stirred solution of NaH (1.5 mmol) in dry THF (5 cm^3) at 0 °C was added portionwise a solution of *rel*-(1*R*)-1-(1-methyl-cyclohexa-2,5-dienyl)-2-((*R*)-2-methyl-propane-2-sulfinyl)-ethanol **83b** (0.326 g, 1.36 mmol) in THF (10 cm^3). Allyl bromide

(0.12 cm^3, 1.36 mmol) was added after 2 h at 0 °C. The reaction was allowed to warm to room temperature overnight. The reaction was quenched with water (30 cm^3) and the aqueous layer was then extracted with diethyl ether (3×50 cm^3). The combined organic layer was dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography (diethyl ether) to give the *title compound* **166** (0.321 g, 84%) as a pink oil; R_f=0.25 (diethyl ether); υ_{max} (neat)/cm^{-1} 2962, 1646, 1460, 1079, 1045; δ_H (360 MHz, $CDCl_3$) 1.19 (9H, s, $(CH_3)_3C$), 1.20 (3H, s, CH_3), 2.35 (2H, dd, *J* 2.9 and *J* 13.7, $CHCH_2CH,CH_2S$), 2.48-2.98 (2H, m, $CHCH_2CH,CH_2S$), 3.56 (1H, dd, *J* 6.6 and 3.0, $CHCH_2S$), 3.92-3.98 (1H, m, OCH_2CH), 4.20 (1H, dd, *J* 12.8 and 5.1, OCH_2CH), 5.16 (1H, d, *J* 10.4, OCH_2CHCH_2), 5.35 (1H, dd, *J* 17.2 and *J* 1.7, OCH_2CHCH_2), 5.48 (1H, dd, *J* 10.2 and 2.9, OCH_2CHCH_2), 5.70-5.94 (4H, m, 2×*CHCH*); δ_C (90 MHz, $CDCl_3$) 22.8 (3×q), 26.3 (q), 26.6 (t), 42.1 (s), 50.1 (t), 53.2 (s), 70.8 (t), 80.6 (d), 117.1 (t), 125.1 (d), 124.1 (d), 129.2 (d), 131.6 (d), 134.5 (d); *m/z* (EI) 282 (M^+; 90%), 169 (63), 119 (88), 91 (100); HR (ESI) 283.1744 (M^+H $C_{16}H_{27}O_2S$ requires 283.1732).

Rel-(2*R*-4*S*-5*R*)-5-methyl-2-(1-methyl-cyclohexa-2,5-dienyl)-[1,4]oxathiane-4-oxide (168) and _rel_-(2*R*-4*R*-5*S*)-5-methyl-2-(1-methyl-cyclohexa-2,5-dienyl)-[1,4]oxathiane-4-oxide (169)



168

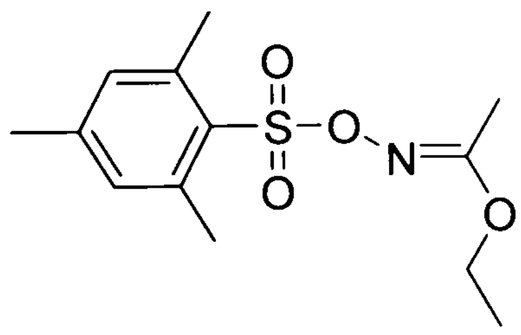


169

A solution of *rel*-(*R*)-3-[1-allyloxy-2-((*R*)-2-methyl-propane-2-sulfinyl)-ethyl]-3-methyl-cyclohexa-1,4-diene **166** (0.065 g, 0.23 mmol) in refluxing xylene (0.14 M) was kept under nitrogen for 3 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by

column chromatography (7:3 diethyl ether/60-80 °C petroleum ether) afforded the *title compound* **168** (0.034 g, 65%) as a white solid followed by the *title compound* **169** (0.014 g, 27%) as a colourless oil; **168** R_f=0.25 (7:3 diethyl ether/60-80 °C petroleum ether); mp 105 °C; υ_{max} (neat)/cm^{-1} 1641, 1443, 1050; δ_H (500 MHz, $CDCl_3$) 1.14 (3H, s, 7'-H), 1.16 (3H, d, *J* 6.2, 7-H), 2.37 (1H, dd, *J* 14.3 and 11.5, 3-H), 2.49-2.55 (1H, m, 5-H), 2.58-2.64 (2H, m, 4'-H), 2.93 (1H, d, *J* 14.3, 3-H), 3.76 (1H, dd, *J* 3.9 and 12.6, 6-H), 3.87 (1H, dd, *J* 11.3 and 1.1, 2-H), 4.00-4.04 (1H, m, 6-H), 5.35-5.39 (1H, m, 2'-H), 5.56-5.59 (1H, m, 6'-H), 5.74-5.79 (2H, m, 3',5'-H); δ_C (125 MHz, $CDCl_3$) 11.5 (7-C), 26.1 (7'-C), 26.5 (4'-C), 39.8 (1'-C), 46.7 (3-C), 47.6 (5-C), 64.5 (6-C), 72.3 (2-C), 125.0 (3'-C), 125.2 (6'-C), 129.1 (2'-C), 130.6 (5'-C); **169** R_f=0.2 (7:3 diethyl ether/60-80 °C petroleum ether); υ_{max} (neat)/cm^{-1} 1455, 1111, 1043; δ_H (500 MHz, $CDCl_3$) 1.16 (3H, s, 7'-H), 1.44 (3H, d, *J* 6.9, 7-H), 2.59-2.64 (3H, m, 3,5,4'-H), 3.06-3.12 (3H, m, 3,4',2-H), 3.62 (1H, dd, *J* 13.4 and 1.9, 6-H), 4.11 (1H, dd, *J* 13.3 and 2.6, 6-H), 5.33-5.36 (1H, m, 2'-H), 5.61-5.63 (1H, m, 6'-H), 5.82-5.86 (4H, m, 3',5'-H); δ_C (125 MHz, $CDCl_3$) 5.1 (7-C), 26.0 (7'-C), 26.6 (4'-C), 40.7 (1'-C), 45.8 (3-C), 48.9 (5-C), 67.8 (6-C), 81.1 (2-C), 125.7 (3'-C), 126.0 (6'-C), 128.1 (2'-C), 130.0 (5'-C); *m/z* (EI) 227 (M^+H; 5%), 104 (42), 93 (96), 90 (100); HR (ESI) 249.0923 (M^+Na $C_{12}H_{18}O_2SNa$ requires 249.0920).

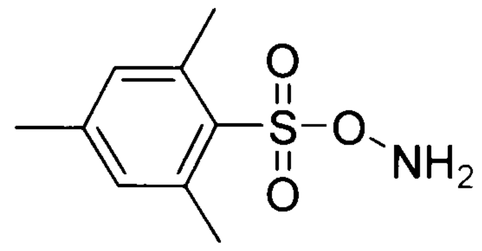
Ethyl-*O*-(mesityl-sulfonyl)acetohydroxamate[89]



Mesitylenesulfonyl chloride (4.59 g, 21 mmol) was added portionwise to a solution of ethyl-N-hydroxyacetimidate (2.2 g, 21 mmol) and triethylamine (3 cm^3, 21 mmol) in anhydrous *N*,*N*-dimethylformamide (6 cm^3) under ice cooling. After 0.5 h at this temperature, the mixture was poured into ice/water. The white precipitate was collected and recrystalised from 60-80 °C petroleum ether to isolate the *title compound* (3.155 g,

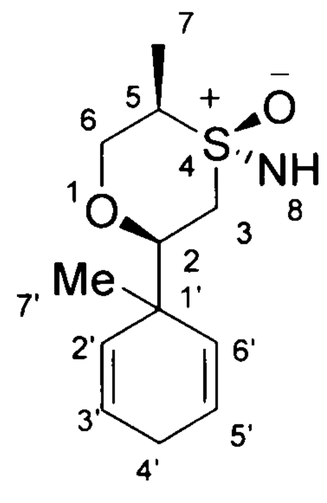
53%). δ_H (360 MHz, $CDCl_3$) 1.21 (3H, t, *J* 7.1), 2.06 (3H, s), 2.33 (3H, s), 2.67 (6H, s), 3.92 (2H, q, *J* 7.1), 6.99 (2H, s).

_O_-mesitylsulfonylhydroxylamine[89]



Ethyl-*O*-(mesityl-sulfonyl)acetohydroxamate (3.15 g, 11 mmol) was dissolved in dioxane (2.1 cm^3) and cooled to 0 °C with stirring. To this was added 70% perchloric acid (1.2 cm^3) dropwise at a rate so as to maintain the temperature below 10 °C. The resulting mixture was added to ice/water (150 cm^3), the crude MSH was filtered off, washed well with distilled water (5×20 cm^3), and dissolved in diethyl ether (15 cm^3). The ether solution was washed with water (13 cm^3), treated with anhydrous potassium carbonate (2 g) for 30 seconds and filtered. The ether solution was poured into cold pentane (150 cm^3) to precipitate the MSH as small crystals (0.89 g, 40%) which were collected and dried *in vacuo*, δ_H (360 MHz, $CDCl_3$) 7.00 (2H, s), 2.65 (6H, s), 2.33 (3H, s), 1.31-0.86 (2H, m).

Rel-(2*R*-4*S*-5*R*)-5-methyl-2-(1-methyl-cyclohexa-2,5-dienyl)-4-oxo-4λ^6-[1,4]oxathian-4-ylamine (170)

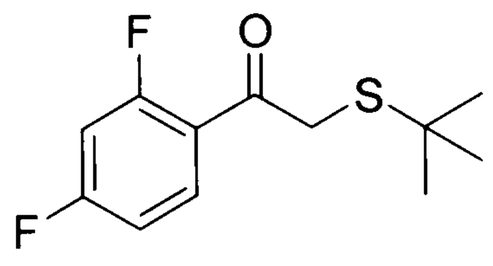


170

O-Mesitylsulfonylhydroxylamine (MSH) (0.12 g, 0.56 mmol) was added to a solution of *rel*-(2*R*-4*S*-5*R*)-5-methyl-2-(1-methyl-cyclohexa-2,5-dienyl)-[1,4]oxathiane-4-oxide **168**

(0.09 g, 0.4 mmol) in dichloromethane (0.5 cm^3) at room temperature. After one day, the solution turned from pale white to yellow. The reaction mixture was poured into cold aqueous 10% NaOH solution (1-2 cm^3), stirred for 10 minutes, and extracted with dichloromethane (3×20 cm^3). The extracts were then washed with 10% HCl solution (2×20 cm^3), and distilled water (2×20 cm^3). The acidic aqueous layer was then neutralised with solid Na_2CO_3, extracted with dichloromethane (3×20 cm^3) and dried over $MgSO_4$. Evaporation of the solvent afforded the *title compound* **170** as a white solid (0.036 g, 39%) which could be crystallised by slow evaporation from ethyl acetate; R_f=0.3 (7:3 diethyl ether/60-80 °C petroleum ether), υ_{max} (neat)/cm^{-1} 3418, 1659, 1633, 1452, 1430; δ_H (500 MHz, $CDCl_3$) 1.17 (3H, s, 7'-H), 1.22 (3H, s, 7-H), 2.56-2.63 (2H, m, 4'-H), 2.68 (1H, bs, 8-H), 2.95 (1H, dd, *J* 2.6 and 11.4, 3-H), 3.01-3.09 (1H, m, 5-H), 3.13 (1H, *J* 1.6 and 12.5, 3-H), 3.58-3.65 (2H, m, 6,2-H), 4.05 (1H, dd, *J* 4.1 and 8.5, 6-H), 5.35-5.38 (1H, m, 2'), 5.58-5.61 (1H, m,6'-H), , 5.80-5.84 (2H, m, 3',5'-H); δ_C (125 MHz, $CDCl_3$) 5.6 (7-C), 26.0 (7'-C), 26.5 (4'-C), 40.1 (1'-C), 55.4 (3-C), 57.7 (5-C), 70.5 (6-C), 81.8 (2-C), 125.5,126.1 (3',5'-C), 128.4,130.0 (2',6'-C).

2-*tert*-Butylsulfanyl-1-(2,4-difluoro-phenyl)-ethanone (179)[91]

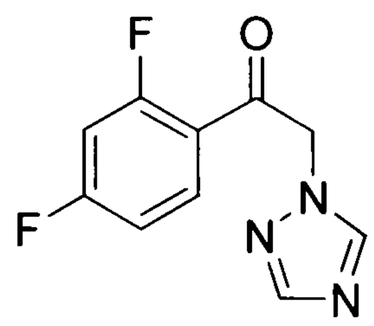


179

Potassium carbonate (0.84 g, 6.11 mmol) was added to a solution of 2-chloro-2',4'-difluoro acetophenone (0.970 g, 5.09 mmol) and *t*-butyl thiol (0.63 cm^3, 5.6 mmol) in methanol (10 cm^3) at 0 °C. The mixture was stirred at room temperature for two hours. After filtration, most of the solvent was removed *in vacuo*. The residue was poured into distilled water (10 cm^3) and extracted with chloroform (3×10 cm^3). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo* to afford the title compound **179** as a yellow oil (1.19 g, 95%); analytical data agree with literature

values;[81] δ_H (360 MHz, $CDCl_3$) 1.32 (9H, s, $(CH_3)_3CS$), 3.88 (2H, d, CH_2S), 6.85-7.01 (2H, m, Ar-H), 7.93 (1H, m, Ar-H); δ_C (90 MHz, $CDCl_3$) 31.2 (q), 40.5 (t), 43.8 (s), 105.1 (d), 112.7 (d), 133.7 (d).

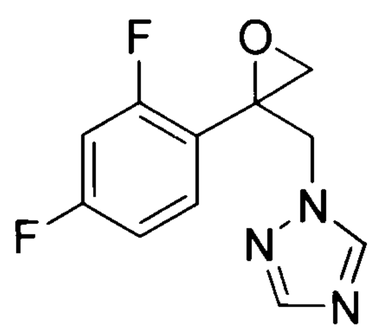
1-(2,4-Difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone (177)[92]



177

A mixture of 4-amino-1,2,4-triazole (1.95 g, 23.2 mmol), 2-chloro-2',4'-difluoro acetophenone (4.219 g, 22.0 mmol) and isopropyl alcohol (44 cm^3) was heated at reflux for 7 h. The reaction mixture was then concentrated by distillation, the isopropyl alcohol removed was replaced with distilled water (44 cm^3), and the reaction mixture was cooled to 5 °C. Concentrated HCl (4.0 cm^3, 48.4 mmol) was added, followed by dropwise addition of saturated aqueous $NaNO_2$ solution (6.7 cm^3, 24.2 mmol). The reaction mixture was allowed to warm to room temperature, and then it was neutralised with K_2CO_3. The product was isolated by filtration, washed with water (20 cm^3), and dried to afford the title compound **177** as a yellow powder (3.9 g, 79%), R_f=0.3 (diethyl ether); δ_H (360 MHz, $CDCl_3$) 5.59 (2H, s), 7.02 (2H, m), 8.04 (2H, m), 8.21 (1H, s); δ_C (90 MHz, $CDCl_3$) 58.8 (t), 105.4 (d), 113.7 (d), 119.4 (s), 133.6 (d), 145.4 (s), 152.4 (d), 165.9 (s), 188.0 (s).

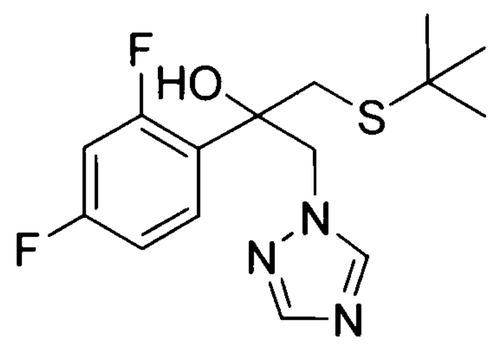
1-[2-(2,4-Difluoro-phenyl)-oxiranylmethyl]-1*H*-[1,2,4]triazole (176)



176

A solution of 1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone **177** (0.984 g, 4.4 mmol) in toluene (6.5 cm^3) was stirred in 20% w/w solution of NaOH (6.5 cm^3). To the mixture trimethylsulfoxonium iodide (0.97 g, 4.4 mmol) and cetrimonium bromide (0.05 g, 0.13 mmol) was added. The reaction solution was stirred at 60 °C for 2 h. The reaction vessel was then allowed to cool to room temperature. The organic layer was then separate and distilled water (10 cm^3) was added to the aqueous layer and extracted with ethyl acetate (2×20 cm^3). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by column chromatography (5% Et_3N in diethyl ether) to afford the *title compound* **176** as a pale yellow oil (0.59 g, 57%), R_f=0.25 (diethyl ether); υ_{max} (neat)/cm^{-1} 1621, 1504, 1274, 1139, 966; δ_H (400 MHz, $CDCl_3$) 2.89 (1H, d, *J* 4.7, NCH_2), 2.94 (1H, d, *J* 4.7, NCH_2), 4.49 (1H, d, *J* 13.8, OCH_2), 4.81 (1H, d, *J* 14.9, OCH_2), 6.81-6.86 (2H, m, Ar-H), 7.16-7.21 (1H, m, Ar-H), 7.85-7.93 (1H, s, NC*H*N), 8.06 (1H, s, NC*H*N); δ_C (90 MHz, $CDCl_3$) 51.2 (t), 52.6 (t), 55.3 (s), 103.2 (d, *J* 25.6), 110.8 (d, *J* 3.7 and 21.6), 118.5 (d, *J* 3.8 and 18.8), 128.6 (d, *J* 5.4 and 9.7), 143.2 (d), 150.9 (d), 159.5 (s, *J* 10.4 and 247.8), 161.8 (s, *J* 11.7 and 250.9); *m/z* (EI) 238 (M^+H, 5%), 214 (16), 162 (10); HR (ESI) 475.1499 (M^+H $C_{22}H_{19}F_4N_6O_2$ requires 475.1500).

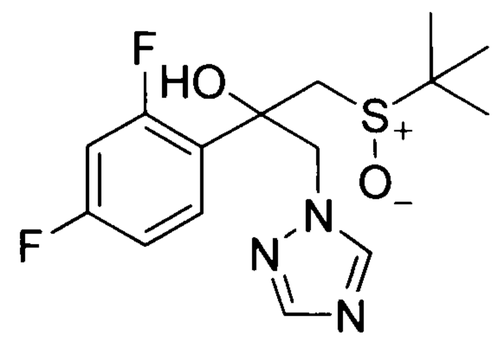
1-*tert*-Butylsulfanyl-2-(2,4-difluoro-phenyl)-3-[1,2,4]triazol-1-yl-propan-2-ol (175)



175

The solvents required for this reaction were deoxygenated prior to use by the rapid passage of nitrogen through the solvent for not less than 30 min. A solution of 1-[2-(2,4-difluoro-phenyl)-oxiranylmethyl]-1*H*-[1,2,4]triazole **176** (0.770 g, 3.2 mmol) in *t*-BuOH (15 cm^3) was mixed with a 0.5 N aqueous NaOH solution (15 cm^3) in a preheated (70 °C) oil bath. The reaction mixture was stirred vigorously as a dropwise addition of a solution of *t*-butyl thiol (0.47 cm^3, 4.2 mmol) in *t*-BuOH (4 cm^3) was conducted over a period of 30 min. During this time the oil bath temperature rose to 78 °C. Stirring was continued for 20 min after the dropwise addition was complete. The reaction mixture was then cooled to room temperature and neutralized with a saturated aqueous NH_4Cl solution. Sufficient distilled water was then added to clarify the aqueous phase, and the phases were then separated. The aqueous phase was extracted with dichloromethane (5×30 cm^3), and the combined organic phases were washed with saturated aqueous NH_4Cl (50 cm^3), dried over $MgSO_4$, concentrated to afford the *title compound* **175** as a white solid (0.940 g, 90%), R_f=0.2 (diethyl ether); mp 98 °C; υ_{max} (neat)/cm^{-1} 3423, 1618, 1500, 1273, 1137, 965; δ_H (360 MHz, $CDCl_3$) 1.24 (9H, s, $(CH_3)_3C$), 2.83 (1H, d, *J* 12.8, SCH_2), 3.36 (1H, d, *J* 12.8, SCH_2), 4.25 (1H, s, OH), 4.66 (2H, s, NCH_2COH), 6.76-6.84 (2H, m, Ar-H), 7.44-7.51 (1H, m, Ar-H), 7.83 (1H, s, NC*H*N), 8.08 (1H, s, NC*H*N); δ_C (100 MHz, $CDCl_3$) 31.2 (3×q), 37.4 (t), 43.2 (s), 56.9 (t), 74.0 (s), 104.5 (d, *J* 25.8 and 27.5), 111.9 (d, *J* 3.2 and 20.5), 130.2 (d, *J* 5.7 and 9.5), 144.9 (d), 151.9 (d), 159.2 (s, *J* 11.5 and 246.7), 163.8 (s, *J* 12.3 and 250.6); *m/z* (EI) 328 (M^+H, 22%), 280 (6), 252 (100); HR (ESI) 350.1115 (M^+Na $C_{15}H_{19}F_2N_3ONa$ requires 350.1109).

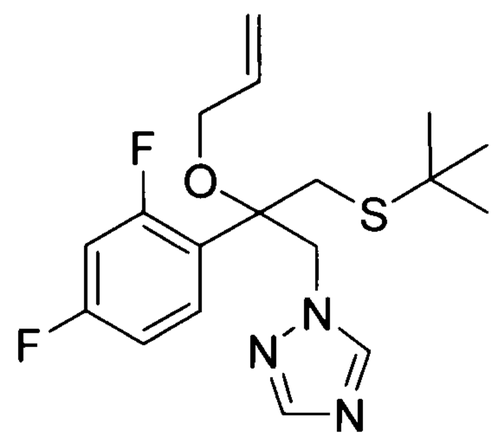
2-(2,4-Difluoro-phenyl)-1-(2-methyl-propane-2-sulfinyl)-3-[1,2,4]triazol-1-yl-propan-2-ol (174)



174

A 27% H_2O_2 solution (0.14 cm^3, 1.08 mmol) was added dropwise to a stirred solution of 1-*tert*-butylsulfanyl-2-(2,4-difluoro-phenyl)-3-[1,2,4]triazol-1-yl-propan-2-ol **175** (0.352 g, 1.08 mmol) in acetic acid (1 cm^3). The reaction was left to go to completion at room temperature overnight. The reaction mixture was dilute in dichloromethane (20 cm^3) and treated with 1 M aqueous NaOH solution (2×10 cm^3). The organic phase was dried over $MgSO_4$ and concentrated to afford the *title compound* **174** as a white solid (0.293 g, 80%, dr 6:1), R_f=0.2 (5:95 methanol/diethyl ether); mp 134 °C; υ_{max} (neat)/cm^{-1} 1498, 1377, 1144; major diastereoisomer δ_H (360 MHz, $CDCl_3$) 1.17 (9H, s, $(CH_3)_3C$), 2.60 (1H, d, *J* 12.5, SCH_2), 3.32 (1H, d, *J* 1.3, SCH_2), 4.33 (1H, d, *J* 14.2, NCH_2COH), 4.63 (1H, dd, *J* 1.8 and 14.16, NCH_2COH), 5.90 (1H, d, *J* 1.6, OH), 6.81-7.00 (2H, m, Ar-H), 7.70-7.90 (1H, m, Ar-H), 8.14 (1H, s, NC*H*N), 8.22 (1H, s, NC*H*N); δ_C (90 MHz, $CDCl_3$) 22.7 (3×q), 48.1 (t), 54.2 (s), 58.7 (t), 75.1 (s), 104.8 (d, *J* 26.2), 112.7 (d, *J* 20.7), 128.6 (s), 130.9 (d, *J* 5.6 and 9.8), 145.6 (d), 151.8 (d), 159.2 (s, *J* 11.7 and 246.1), 162.2 (s, *J* 11.2 and 242.6); *m/z* (EI) 344 (M^+H, 100%), 252 (10); HR (ESI) 366.1070 (M^+Na $C_{15}H_{19}F_2N_3O_2SNa$ requires 366.1060).

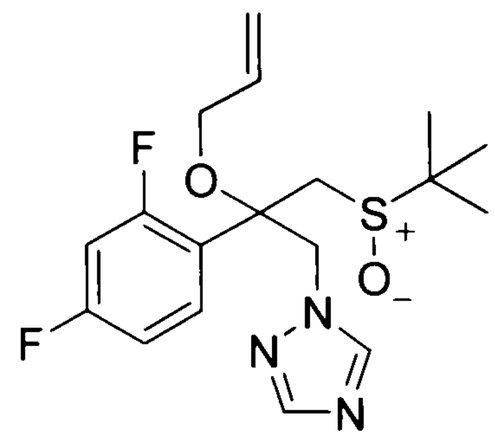
1-[3-Allyloxy-4-*tert*-butylsulfanyl-2-(2,4-difluoro-phenyl)-butyl]-1*H*-[1,2,4]triazole (180)



180

A solution of 2-(2,4-difluoro-phenyl)-1-(2-methyl-propane-2-sulfinyl)-3-[1,2,4]triazol-1-yl-propan-2-ol **175** (0.54 g, 1.6 mmol) in anhydrous *N*,*N*-dimethylformamide (2 cm^3) was added dropwise to sodium hydride (3.2 mmol) in *N*,*N*-dimethylformamide (4 cm^3) at 0 °C. The reaction was stirred at 0 °C for 1 h, after which time a solution of allyl bromide (0.17 cm^3, 1.92 mmol) and tetra-butyl ammonium iodide (0.059 g, 0.16 mmol) in *N*,*N*-dimethylformamide (1 cm^3) was added dropwise to the orange solution. The reaction mixture was allowed to reach to room temperature. After two hours, the reaction mixture was diluted in ethyl acetate (10 cm^3). The organic layer was washed with H_2O (3×10 cm^3), dried over $MgSO_4$, and concentrated *in vacuo* to afford the *title compound* **180** as a yellow oil (0.54 g, 92%), R_f=0.25 (5:95 methanol/diethyl ether); υ_{max} (neat)/cm^{-1} 1600, 1500, 1150, 1050; δ_H (360 MHz, $CDCl_3$) 1.34 (9H, s, $(CH_3)_3C$), 3.30 (2H, dd, *J* 13.2 and 25.0, SCH_2), 3.96-4.01 (1H, m, OCH_2), 4.21-4.25 (1H, m, OCH_2), 4.70 (1H, d, *J* 14.4, NCH_2), 4.80 (1H, d, *J* 14.4, NCH_2), 5.22 (1H, dd, *J* 1.40 and 10.5, OCH_2CHCH_2), 5.35 (1H, dd, *J* 1.66 and 17.2, OCH_2CHCH_2), 5.92-6.00 (1H, m, OCH_2CHCH_2), 6.75-6.85 (2H, m, Ar-H), 7.06-7.12 (1H, m, Ar-H), 7.69 (1H, s, NC*H*N), 7.98 (1H, s, NC*H*N); δ_C (90 MHz, $CDCl_3$) 31.4 (3×q), 33.3 (t), 43.0 (s), 55.3 (t), 64.8 (t), 79.0 (s), 105.3 (d, *J* 25.2 and 28.3), 112.0 (d, *J* 23.9), 117.6 (t), 130.5 (d, *J* 5.5 and 9.3), 134.1 (d), 144.9 (d), 151.6 (d); *m/z* (EI) 368 (M^+H, 10%), 264 (100), 222 (90), 57 (70); HR (ESI) 390.1410 (M^+Na $C_{18}H_{23}F_2N_3OSNa$ requires 390.1422).

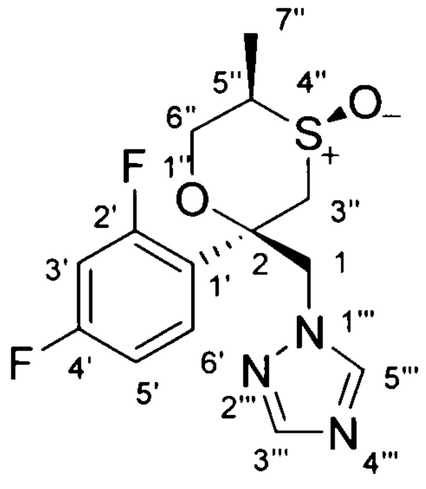
1-[3-Allyloxy-2-(2,4-difluoro-phenyl)-4-(2-methyl-propane-2-sulfinyl)-butyl]-1*H*-[1,2,4]triazole (173)



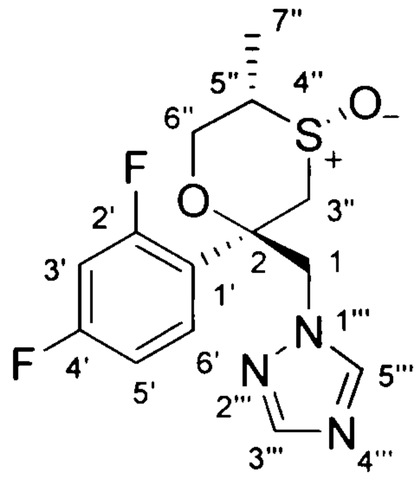
173

A 27% aqueous hydrogen peroxide solution (0.50 cm^3, 4.4 mmol) was added dropwise to a stirred solution of 1-[3-allyloxy-4-*tert*-butylsulfanyl-2-(2,4-difluoro-phenyl)-butyl]-1*H*-[1,2,4]triazole **180** (1.63 g, 4.4 mmol) in acetic acid (5 cm^3) at 10 °C. Stirring was continued at room temperature for 15 h and the solvent was then removed *in vacuo*. The crude product was purified by column chromatography (5% MeOH in diethyl ether) to yield the *title compound* **173** as a colourless oil (1.17 g, 69%, dr 1.5:1); **173** R_f=0.25 (5:95 methanol/diethyl ether); υ_{max} (neat)/cm^{-1} 1615, 1505, 1298, 1139, 965; δ_H (360 MHz, $CDCl_3$) 1.26 (9H, s, $(CH_3)_3C$), 1.27 (9H, s, $(CH_3)_3C$), 3.03 (1H, d, *J* 14.0, SCH_2), 3.27 (2H, s, SCH_2), 3.35 (1H, d, *J* 14.0, SCH_2), 4.10-4.22 (4H, m, OCH_2), 4.83-4.95 (4H, m, NCH_2), 5.12-5.41 (6H, m, OCH_2CHCH_2, NCH_2), 5.92-6.03 (2H, m, OCH_2CHCH_2), 6.79-6.91 (4H, m, Ar-H), 7.19-7.30 (2H, m, Ar-H), 7.68 (1H, s, NC*H*N), 7.85 (1H, s, NC*H*N), 8.11 (1H, s, NC*H*N), 8.21 (1H, s, NC*H*N); δ_C (100 MHz, $CDCl_3$) 22.8 (6×q), 50.4 (t), 51.4 (t), 53.0 (t), 54.0 (t), 54.9 (2×s), 64.5 (t), 64.5 (t), 64.8 (t), 104.7 (d, *J* 27.0), 105.3 (d, *J* 25.0), 111.8 (d, *J* 17.6), 112.0 (d, *J* 17.1), 117.5 (2×t), 129.6 (d, *J* 11.2), 129.8 (d, *J* 5.2), 132.9 (d), 133.4 (d), 144.7 (d), 145.4 (d), 151.0 (d), 151.5 (d), 160.3 (s, *J* 21.4 and 242.6), 160.7 (s, *J* 12.3 and 251.1), 161.9 (s, *J* 12.3 and 242.0), 163.2 (s, *J* 12.3 and 230.4); *m/z* (EI) 383 (M^+, 5%), 327 (61), 71 (56), 57 (100); HR (ESI) 384.1573 (M^+H $C_{18}H_{24}F_2N_3OS$ requires 390.1552).

***Rel*-(2*R*,4*S*,5*R*)-1-[2-(2,4-difluoro-phenyl)-5-methyl-4-oxo-4λ^4-[1,4]oxathian-2-ylmethyl]-1*H*-[1,2,4]triazole (162) and *rel*-(2*R*,4*R*,5*S*)-1-[2-(2,4-difluoro-phenyl)-5-methyl-4-oxo-4λ^4-[1,4]oxathian-2-ylmethyl]-1*H*-[1,2,4]triazole (163)**



162

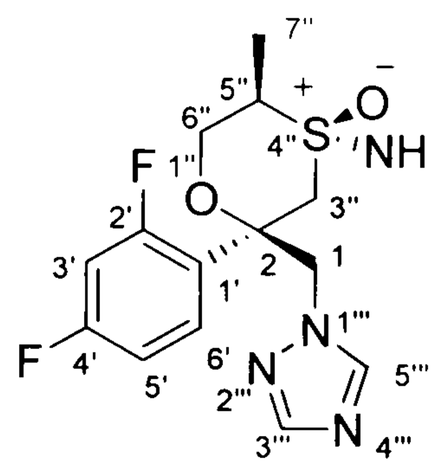


163

A solution of 1-[3-allyloxy-2-(2,4-difluoro-phenyl)-4-(2-methyl-propane-2-sulfinyl)-butyl]-1*H*-[1,2,4]triazole **173** (1.14 g, 2.97 mmol) was placed under an inert atmosphere of argon and refluxed in xylene (0.14 M) for 1 h. The reaction vessel was then allowed to cool to room temperature and the content of the flask was loaded onto a column of silica gel. Purification by column chromatography (5:95 methanol/diethyl ether) afforded the *title compound* **162** as a white solid (0.32 g, 33%), which could be crystallised by slow evaporation of dichloromethane, and followed by the *title compound* **163** as a white solid (0.5 g, 51%); **162** R_f=0.5 (2:8 methanol/diethyl ether); mp 195 °C, υ_{max} (neat)/cm^{-1} 1619, 1501, 1140, 1104; δ_H (500 MHz, $CDCl_3$) 1.34 (3H, d, *J* 7.1, 7``-H), 2.83-2.92 (2H, m, 5``,6``-H), 3.67 (1H, d, *J* 14.6, 6``-H), 3.97 (1H, dd, *J* 3.4 and 13.4, 3``-H), 4.60 (1H, dd, *J* 9.3 and 13.4, 3``-H), 4.68 (1H, d, *J* 15.4, 1-H), 5.60 (1H, d, *J* 15.3, 1-H), 6.76-6.90 (2H, m, Ar-H), 7.22-7.28 (1H, m, Ar-H), 7.71 (2H, d, *J* 12.6, 3```,5```-H); δ_C (125 MHz, $CDCl_3$) 10.6 (q), 48.0 (d), 48.4 (t), 52.4 (t), 59.3 (t), 75.3 (s), 105.1 (d, *J* 26.4), 112.3 (d, *J* 14.9 and 18.7), 129.2 (d, *J* 7.5 and 13.1), 144.1 (d), 151.6 (d), 159.6 (s, *J* 12.0 and 248.9), 163.3 (s, *J* 12.8 and 252.0); *m/z* (EI) 328 (M^+H, 25%), 245 (100), 141 (75); HR (ESI) 350.0743 (M^+Na $C_{14}H_{15}F_2N_3O_2SNa$ requires 350.0745); **163** R_f=0.3 (2:8 methanol/diethyl ether); mp 220 °C; υ_{max} (neat)/cm^{-1} 1618, 1501, 1140, 1097, 1031; δ_H (500 MHz, $CDCl_3$) 1.12 (3H, d, *J* 7.09, 7``-H), 2.49 (1H, d, *J* 4.09, 3``-H), 2.58-2.64 (1H, m, 5``-H), 3.77 (1H, dd, *J* 3.62 and 12.9, 6``-H), 4.16-4.21 (2H, m, 3``,6``-H), 4.28 (1H,

d, *J* 14.4, 1-H), 4.39 (1H, d, *J* 14.4, 1-H), 6.82-6.92 (2H, m, Ar-H), 7.31-7.38 (1H, m, Ar-H), 7.88 (1H, s, NC*H*N), 8.01 (1H, s, NC*H*N); δ_C (125 MHz, $CDCl_3$) 11.6 (q), 46.7 (t), 46.8 (t), 48.0 (d), 73.6 (s), 105.5 (d, *J* 27.8, 25.4), 112.2 (d, *J* 21.0), 121.3 (s, *J* 4.0 and 11.6), 128.8 (d, *J* 4.9), 145.3 (d), 151.9 (d), 159.5 (s), 160.7 (s, *J* 9.3 and 237.2), 163.6 (s, *J* 12.6 and 242.8); *m/z* (EI) 328 (M^+H, 12%), 280 (17), 252 (12); HR (ESI) 350.0752 (M^+Na $C_{14}H_{15}F_2N_3O_2SNa$ requires 350.0745).

Rel-(2*R*,4*S*,5*R*)-2-(2,4-difluoro-phenyl)-5-methyl-4-oxo-2-[1,2,4]triazol-1-ylmethyl-4λ^6-[1,4]oxathian-4-ylideneamine (164)

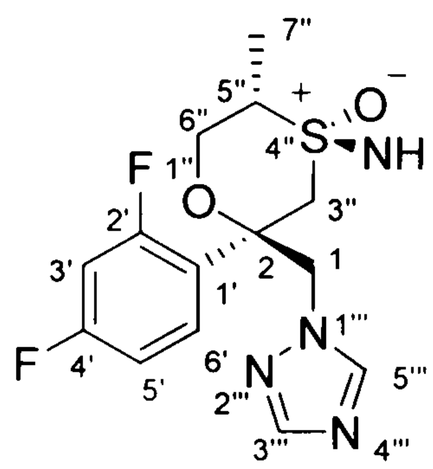


164

In a flask equipped with a condenser, a mixture of *rel*-(2*R*,4*S*,5R)-1-[2-(2,4-difluoro-phenyl)-5-methyl-4-oxo-4λ^4-[1,4]oxathian-2-ylmethyl]-1*H*-[1,2,4]triazole **162** (0.072 g, 0.22 mmol), sodium azide (0.016 g, 0.24 mmol) in anhydrous chloroform (1 cm^3) was cooled in an ice bath. To this slurry solution, concentrated sulfuric acid (0.25 cm^3) was added over a period of 5 minutes. After cooling, distilled water (3 cm^3) was added. After all the salts were dissolved, chloroform was separated and the aqueous layer was re-extracted with chloroform (3×20 cm^3). The aqueous layer was made slightly alkaline with a 20% NaOH solution, extracted with chloroform (2×20 cm^3), and dried over $MgSO_4$. Purification by column chromatography (4:96 methanol/diethyl ether) afforded the starting material **162** (0.027 g, 37%), followed by the *title compound* **164** as a white solid (0.015 g, 20%); R_f=0.25 (4:96 methanol/diethyl ether); mp 64 °C; υ_{max} (neat)/cm^{-1} 3435, 2335, 1635, 1495, 1270, 1177; δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d, *J* 7.1, 7''-H), 2.64-2.68 (1H, m, 5''-H), 3.16 (1H, d, *J* 14.3, 1-H), 3.40 (1H, s, NH), 3.41 (1H, d, *J* 14.4, 1-

H), 3.83 (1H, dd, *J* 5.6 and 13.4, 6``-H), 4.37-4.63 (3H, m, 3``,6``-H), 6.79-6.91 (2H, m, Ar-H), 7.25-7.35 (1H, m, Ar-H), 7.77 (2H, d, *J* 8.3, 3```,5```-H); δ_C (100 MHz, $CDCl_3$) 11.8 (q), 46.4 (t), 52.3 (d), 56.3 (t), 60.5 (t), 76.0 (s), 105.5 (d, *J* 27.5 and 25.7), 112.4 (d, *J* 3.2 and 21.4), 122.1 (s, *J* 3.8 and 11.0), 129.2 (s, *J* 4.9 and 9.4), 144.9 (d), 152.0 (d), 160.6 (s, *J* 11.5 and 248.7), 163.3 (s, *J* 12.6 and 251.6); *m/z* (EI) 327 (9), 245 (100), 141 (83).

Rel-(2*R*,4*R*,5*S*)-2-(2,4-difluoro-phenyl)-5-methyl-4-oxo-2-[1,2,4]triazol-1-ylmethyl-4λ^6-[1,4]oxathian-4-ylideneamine (165)

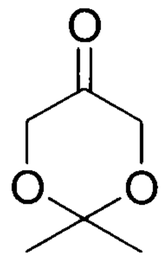


165

O-Mesitylsulfonylhydroxylamine (MSH) (0.28 g, 1.3 mmol) was added to a solution of *rel*-(2*R*,4*R*,5S)-1-[2-(2,4-difluoro-phenyl)-5-methyl-4-oxo-4λ^4-[1,4]oxathian-2-ylmethyl]-1*H*-[1,2,4]triazole **163** (0.14 g, 0.43 mmol) in dichloromethane (1 cm^3) at room temperature. After one day, the solution turned from pale white to yellow. The reaction mixture was poured into cold aqueous 10% NaOH solution (3-4 cm^3), stirred for 10 minutes, and extracted with dichloromethane (3×20 cm^3). The extracts were then washed with 10% HCl solution (2×20 cm^3), and distilled water (2×20 cm^3). The acidic aqueous layer was then neutralised with solid Na_2CO_3, extracted with dichloromethane (3×20 cm^3) and dried over $MgSO_4$. Purification by column chromatography (2:8 methanol/diethyl ether) afforded the starting material **163** (0.05 g, 36%), followed by the *title compound* **165** as a white solid (0.06 g, 41%) which could be crystallised by slow evaporation from ethyl acetate: R_f=0.25 (2:8 methanol/diethyl ether); mp 110 °C; υ_{max} (neat)/cm^{-1} 3429, 1620, 1504, 1217, 1140, 1098, 968; δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d,

J 6.9, 7``-H), 2.87 (1H, bs, NH), 3.13-3.22 (1H, m, 5``-H), 3.28 (1H, d, *J* 14.9, 3``-H), 3.94 (1H, dd, *J* 10.2 and 13.0, 6''-H), 4.13-4.18 (2H, m, 3``,6``-H), 4.37 (1H, d, *J* 14.6, 1-H), 4.57 (1H, d, *J* 14.6, 1-H), 6.86-6.92 (2H, m, Ar-H), 7.21-7.28 (1H, m, Ar-H), 7.86 (1H, s, NC*H*N), 7.94 (1H, s, NC*H*N); δ_C (100 MHz, $CDCl_3$) 6.8 (q), 56.5 (t), 56.6 (d), 58.2 (t), 66.2 (t), 79.2 (s), 105.8 (d, *J* 25.7 and 28.3), 112.5 (d, *J* 3.4 and 21.0), 119.7 (s, *J* 7.7), 129.3 (d, *J* 4.6 and 9.3), 145.1 (d), 152.1 (d), 160.5 (s, *J* 11.5 and 249.0), 163.7 (s, *J* 12.6 and 251.9); *m/z* (EI) 297 (100), 263 (15), 196 (5); HR (ESI) 365.0853 (M^+Na $C_{14}H_{16}F_2N_4O_2SNa$ requires 365.0854).

2,2-Dimethyl-1,3-dioxane-5-one (198)[103]

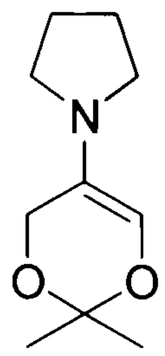


198

A 500 cm^3 round-bottom flask, equipped with a magnetic stirring bar, was filled with 2-amino-2-hydroxymethyl-1,3-propandiol hydrochloride (21.748 g, 138.0 mmol), anhydrous *N*,*N*-dimethylformamide (45 cm^3), 2,2-dimethoxypropane (20.3 cm^3, 165.6 mmol) and camphor sulfonic acid (1.6 g, 6.9 mmol). The mixture was stirred at room temperature for 40 h. Triethylamine (1.2 cm^3) was added followed by removal of the solvent under reduced pressure. The residue was dissolved in ethyl acetate (340 cm^3) and triethylamine (19 cm^3) was stirred at room temperature for 10 min. The precipitate was filtered and the solvent was removed under reduced pressure. The crude ß-amino alcohol (19.952 g, 123.9 mmol) was then transferred to a 1000 cm^3 three necked round-bottom flask, equipped with an overhead stirrer, dropping funnel and thermometer and was dissolved in distilled water (180 cm^3). KH_2PO_4 (39.8 g, 185.9 mmol) was added and the solution was cooled to 5 °C. Then, an aqueous sodium periodate solution (372 cm^3, 0.5 M) was added dropwise over 3 h while the temperature was maintained at 5-10 °C. The cooling bath was removed and the mixture was stirred at room temperature for 15 h. The aqueous solution was extracted with dichloromethane (10×30 cm^3). The combined

organic layers were washed with brine (50 cm^3), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by distillation to afford the title compound **198** as a colourless oil (8.254 g, 52%; 2 steps); bp 50-54 °C/11 Torr; δ_H (360 MHz, $CDCl_3$) 1.46 (6H, s, 2×CH_3), 4.16 (4H, s, 2×CH_2).

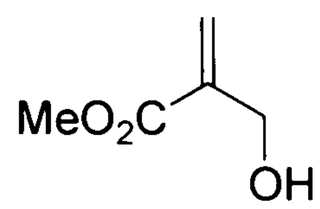
1-(2,2-Dimethyl-4*H*-[1,3]dioxin-5-yl)-pyrrolidine (196)



196

To a solution of 2,2-dimethyl-1,3-dioxane-5-one **198** (2.118 g, 16.3 mmol) in dry toluene (15 cm^3) were added molecular sieves (4Å, 3.4 g) and pyrrolidine (1.35 cm^3, 16.3 mmol). The solution was stirred at room temperature overnight. The mixture was filtered and quenched with saturated NaCl solution (20 cm^3) and extracted with dichloromethane (3×20 cm^3). The combined organic extracts were washed with distilled water (20 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* **196** as a colourless oil (2.512 g, 84%); δ_H (360 MHz, $CDCl_3$) 1.45 (6H, s, 2×CH_3), 1.84 (4H, quintet, *J* 6.7, CH_2CH_2), 2.78 (4H, t, *J* 6.7, CH_2NCH_2), 4.29 (2H, d, *J* 1.3, OCH_2CN), 5.80 (1H, s, OC*H*CN); δ_C (90 MHz, $CDCl_3$) 23.6 (2×t), 24.0 (2×q), 48.5 (2×t), 60.2 (t), 97.6 (s), 120.5 (d), 125.1 (s).

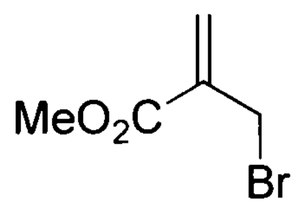
2-Hydroxymethyl-acrylic acid methyl ester (199)[107]



199

Paraformaldehyde (11 g, 366 mmol), 1 N phosphoric acid (1.3 cm^3), and distilled water (33.3 cm^3) were heated at 90 °C for 1.5 h to form a clear aqueous formaldehyde solution. After the solution was cooled to room temperature, THF (33.3 cm^3), methyl acrylate (30 cm^3, 332 mmol), and 1,4-diazabicyclo[2.2.2]octane (3.8 g, 33.9mmol) were added, and the reaction mixture was stirred for 36 h. To the reaction mixture NaCl (12 g) and diethyl ether (30 cm^3) were added. The organic layers were separated and then the product was extracted from the aqueous layer with diethyl ether (3×30 cm^3). The combined organic layers were washed with saturated NaCl solution (2×30 cm^3) and dried over $MgSO_4$: the solvents were evaporated under reduced pressure and the residue was distilled *in vacuo* to afford the title compound **199** as a colourless oil (6.315 g, 16%): bp 65-70 °C/1 mm; δ_H (360 MHz, $CDCl_3$) 2.32 (1H, bs, OH), 3.81 (3H, s, CH_3), 4.35 (2H, s, CH_2OH), 5.86 (1H, s, C*H*), 6.28 (1H, s, C*H*).

2-Bromomethyl-acrylic acid methyl ester (197)

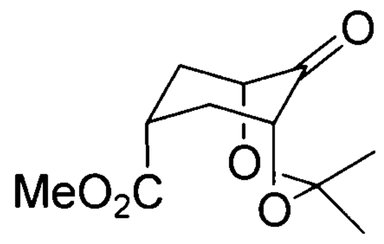


197

Phosphorus bromide (1.05 cm^3, 10.9 mmol) is added to a stirred solution of methyl α-hydroxymethylacrylate **199** (2.533 g, 21.8 mmol) in dry diethyl ether (26 cm^3) at -10 °C. The temperature is allowed to rise to 20 °C and stirring is continued for 3 h. Distilled water (15 cm^3) is then added at -10 °C and the mixture is extracted with hexane (3×20 cm^3). The organic phase is washed with saturated aqueous NaCl (2×20 cm^3) and dried

over $MgSO_4$. The solvents are evaporated and the remaining oil is distilled *in vacuo* to afford the title compound **197** as a colourless oil (2.803 g, 72%); analytical data agree with literature values;[116] bp 86 °C/20 Torr; δ_H (360 MHz, $CDCl_3$) 3.82 (3H, s, CH_3), 4.18 (2H, s, CH_2), 5.96 (1H, s, C*H*), 6.34 (1H, s, C*H*).

3,3-Dimethyl-9-oxo-2,4-dioxa-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester (201)

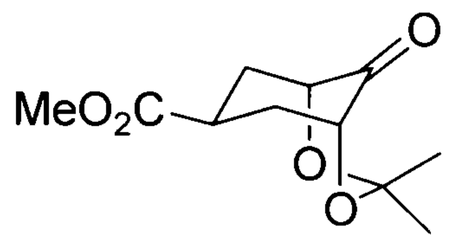


201

To a solution of 1-(2,2-dimethyl-4*H*-[1,3]dioxin-5-yl)-pyrrolidine **196** (2.501 g, 13.7 mmol) and triethylamine (1.9 cm^3) in anhydrous acetonitrile (26 cm^3) was added dropwise with stirring methyl α-bromomethylacrilate **197** (2.400 g, 13.7 mmol) dissolved in acetonitrile (4 cm^3). Heat was generated upon addition and, as the solution turned reddish brown, a solid precipitated. The reaction mixture was heated at reflux for 5 h. Hydrolysis of the iminium ion was accomplished by the addition of 5% aqueous acetic acid (13 cm^3) followed by 1 h reflux period. The reaction was left to cool to room temperature and an equal volume of distilled water was added. The aqueous mixture was then extracted with diethyl ether (5×30 cm^3) and the combined extracts were washed with 5% aqueous hydrochloric acid (40 cm^3), saturated aqueous Na_2CO_3 (30 cm^3), and saturated aqueous NaCl (30 cm^3). The resulting ethereal solution was dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. Purification by column chromatography (5:5 diethyl ether/60-80 °C petroleum ether) afforded the *title compound* **201** as a white solid (1.053 g, 34%); R_f=0.25 (5:5 diethyl ether/60-80 °C petroleum ether); mp 65 °C, υ_{max} (neat)/cm^{-1} 1743, 1452, 1023, 994; δ_H (360 MHz, $CDCl_3$) 1.37 (6H, d, *J* 6.0, 2×CH_3), 1.07 (2H, dd, *J* 7.0 and 14.1, 2×CH_2), 2.59 (1H, t, *J* 7.2, $CHCO_2CH_3$), 3.27 (2H, m, 2×CH_2), 3.77 (3H, s, CO_2CH_3), 4.29 (2H, d, *J* 4.0, 2×C*H*CO); δ_C (90 MHz, $CDCl_3$) 24.1 (q), 27.7 (q), 38.8 (d), 38.6 (2×t), 52.0 (q), 76.7 (2×d), 99.0 (s),

173.6 (s), 215.1 (s); *m/z* (EI) 228 (M^+; 2%), 213 (100), 101 (32), 83 (62); HR (ESI) 251.0896 (M^+Na $C_{11}H_{16}O_5Na$ requires 251.0890).

3,3-Dimethyl-9-oxo-2,4-dioxa-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester (187)

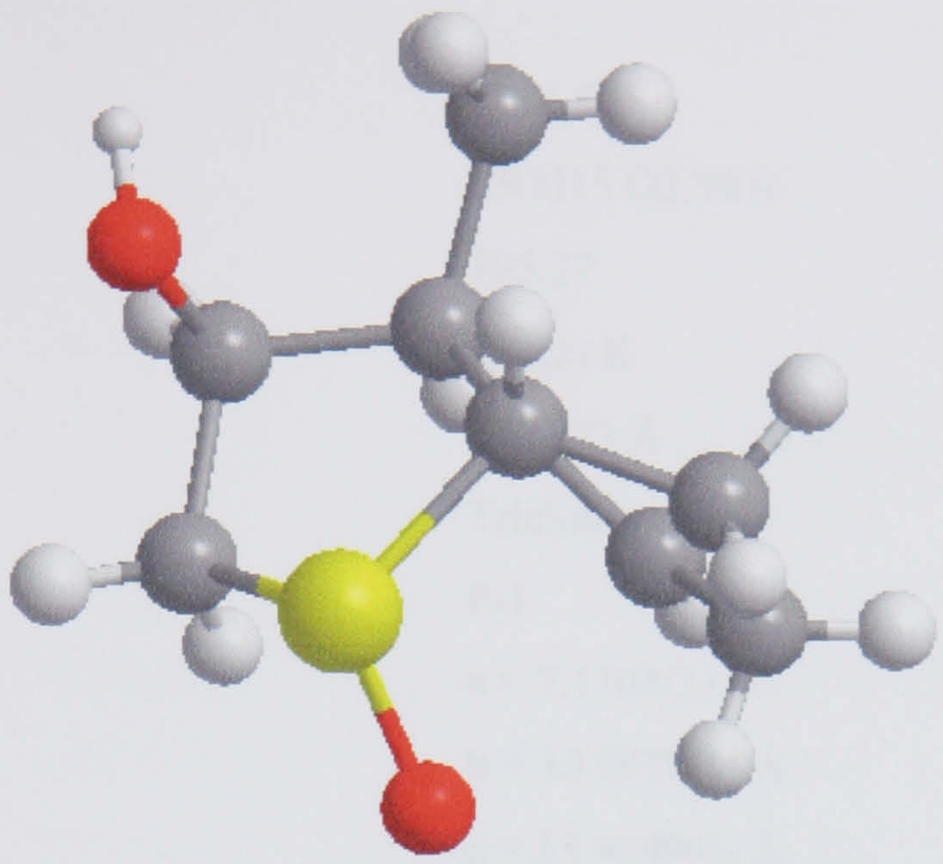


187

To a solution of sodium methoxide (0.89 mmol) in dry methanol (25 cm^3) was added with stirring a solution of the *endo* compound **201** (0.203 g, 0.89 mmol) in dry methanol (25 cm^3). The reaction mixture was heated at reflux overnight, allowed to cool, and neutralised with 10% aqueous acetic acid (10 cm^3). An equal volume of distilled water was added and the resulting mixture was extracted with diethyl ether (5×30 cm^3). The combined extracts were washed with saturated aqueous Na_2CO_3 (30 cm^3) and saturated aqueous NaCl (30 cm^3). The resulting solution was then dried over anhydrous $MgSO_4$. Filtration and evaporation *in vacuo* afforded the *title compound* **187** as a white solid (0.094 g, 47%); R_f=0.35 (5:5 diethyl ether/60-80 °C petroleum ether); mp 80 °C, υ_{max} (neat)/cm^{-1} 1725, 1463, 1009, 960; δ_H (360 MHz, $CDCl_3$) 1.43 (3H, s, C*H*$_3$), 1.52 (3H, s, C*H*$_3$), 1.94 (2H, t, *J* 13.6, 2×C*H*$_2$), 2.59 (2H, m, 2×C*H*$_2$), 3.52 (1H, tt, *J* 4.6 and 12.6, C*H*CO_2CH_3), 3.69 (3H, s, CO_2C*H*$_3$), 4.29 (2H, d, *J* 3.8, 2×C*H*CO); δ_C (90 MHz, $CDCl_3$) 25.1 (q), 28.5 (q), 33.1 (d), 40.3 (2×t), 52.1 (q), 76.1 (2×d), 98.8 (s), 174.3 (s), 214.1 (s); *m/z* (EI) 229 (M^+H; 13%), 213 (56), 114 (87), 55 (100); HR (ESI) 251.0894 (M^+Na $C_{11}H_{16}O_5Na$ requires 251.0890).

Appendices

6.1 X-ray analysis of 91a



91a

Crystal data for **91a**: $C_9H_{15}O_{2.50}S$, M = 195.27, colourless prism, 0.80 0.25 0.20 mm^3, triclinic, space group P-1 (No. 2), a = 7.1304(3), b = 10.9979(4), c = 13.4699(6) Å, α = 109.079(2), β = 92.0540(10), γ = 100.681(2)°, V = 975.68(7) Å^3, Z = 4, D_c = 1.329 g/cm^3, F_{000} = 420, Nonius KappaCCD, MoK radiation, = 0.71073 Å, T = 120(2)K, $2\theta_{max}$ = 54.9°, 3808 reflections collected, 2637 unique (R_{int} = 0.0534). Final *GooF* = 1.047, *R1* = 0.0347, *wR2* = 0.0832, *R* indices based on 2203 reflections with I >2sigma(I) (refinement on F^2), 239 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.298 mm^{-1}.

Table 1. Crystal data and structure refinement for **91a**.

Identification code	C:aA.CIF	
Empirical formula	C9 H15 O2.50 S	
Formula weight	195.27	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.1304(3) Å	α= 109.079(2)°.
	b = 10.9979(4) Å	ß= 92.0540(10)°.
	c = 13.4699(6) Å	γ= 100.681(2)°.
Volume	975.68(7) $Å^3$	
Z	4	
Density (calculated)	1.329 Mg/m^3	
Absorption coefficient	0.298 mm^{-1}	
F(000)	420	
Crystal size	0.80 x 0.25 x 0.20 mm^3	
Theta range for data collection	2.92 to 27.44°.	
Index ranges	-7<=h<=9, -13<=k<=11, -16<=l<=17	
Reflections collected	3808	
Independent reflections	2637 [R(int) = 0.0534]	
Completeness to theta = 27.44°	59.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9429 and 0.7967	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2637 / 0 / 239	
Goodness-of-fit on F^2	1.047	
Final R indices [I>2sigma(I)]	R1 = 0.0347, wR2 = 0.0832	
R indices (all data)	R1 = 0.0475, wR2 = 0.0892	
Extinction coefficient	0.014(3)	
Largest diff. peak and hole	0.436 and -0.358 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **91a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	-8318(1)	3759(1)	1075(1)	22(1)
O(1)	-9108(3)	2967(2)	1760(1)	32(1)
C(1)	-9910(3)	3157(2)	-136(2)	22(1)
S(2)	-3570(1)	3705(1)	-4733(1)	21(1)
O(2)	-7830(2)	4445(2)	-896(1)	22(1)
C(2)	-8594(3)	3116(2)	-1001(2)	19(1)
O(3)	-4976(2)	3045(2)	-4156(1)	27(1)
C(3)	-7028(3)	2410(2)	-788(2)	16(1)
O(4)	-1361(2)	3748(1)	-6703(1)	19(1)
C(4)	-7925(3)	967(2)	-1046(2)	17(1)
O(5)	-6376(3)	4792(2)	-2595(1)	24(1)
C(5)	-7835(3)	284(2)	-407(2)	21(1)
C(6)	-6839(4)	849(2)	689(2)	25(1)
C(7)	-5536(4)	2195(2)	903(2)	23(1)
C(8)	-6336(3)	3071(2)	395(2)	18(1)
C(9)	-5366(3)	2547(2)	-1467(2)	23(1)
C(10)	-4185(3)	2779(2)	-6128(2)	20(1)
C(11)	-2335(3)	2543(2)	-6598(2)	17(1)
C(12)	-1181(3)	2140(2)	-5804(2)	15(1)
C(13)	-2143(3)	779(2)	-5851(2)	18(1)
C(14)	-2568(3)	424(2)	-5022(2)	22(1)
C(15)	-2210(4)	1332(2)	-3911(2)	27(1)
C(16)	-953(4)	2679(2)	-3785(2)	27(1)
C(17)	-1276(3)	3154(2)	-4712(2)	19(1)
C(18)	902(3)	2170(2)	-6050(2)	24(1)

Table 3. Bond lengths [Å] and angles [°] for **91a**.

S(1)-O(1)	1.5180(17)
S(1)-C(1)	1.808(3)
S(1)-C(8)	1.856(2)
C(1)-C(2)	1.517(3)
S(2)-O(3)	1.5135(17)
S(2)-C(10)	1.812(2)
S(2)-C(17)	1.849(2)
O(2)-C(2)	1.420(3)
C(2)-C(3)	1.542(3)
C(3)-C(4)	1.515(3)
C(3)-C(8)	1.537(3)
C(3)-C(9)	1.538(3)
O(4)-C(11)	1.431(3)
C(4)-C(5)	1.321(3)
C(5)-C(6)	1.494(3)
C(6)-C(7)	1.527(3)
C(7)-C(8)	1.526(3)
C(10)-C(11)	1.513(3)
C(11)-C(12)	1.550(3)
C(12)-C(13)	1.507(3)
C(12)-C(18)	1.530(3)
C(12)-C(17)	1.540(3)
C(13)-C(14)	1.325(3)
C(14)-C(15)	1.485(3)
C(15)-C(16)	1.536(3)
C(16)-C(17)	1.528(3)
O(1)-S(1)-C(1)	106.96(11)
O(1)-S(1)-C(8)	109.32(10)
C(1)-S(1)-C(8)	92.57(10)
C(2)-C(1)-S(1)	104.86(16)
O(3)-S(2)-C(10)	106.37(10)
O(3)-S(2)-C(17)	109.95(10)
C(10)-S(2)-C(17)	92.51(10)

O(2)-C(2)-C(1)	106.35(18)
O(2)-C(2)-C(3)	112.08(19)
C(1)-C(2)-C(3)	105.81(18)
C(4)-C(3)-C(8)	111.17(19)
C(4)-C(3)-C(9)	109.48(18)
C(8)-C(3)-C(9)	111.00(19)
C(4)-C(3)-C(2)	108.36(19)
C(8)-C(3)-C(2)	105.45(18)
C(9)-C(3)-C(2)	111.30(19)
C(5)-C(4)-C(3)	125.5(2)
C(4)-C(5)-C(6)	124.0(2)
C(5)-C(6)-C(7)	112.5(2)
C(8)-C(7)-C(6)	114.3(2)
C(7)-C(8)-C(3)	114.62(19)
C(7)-C(8)-S(1)	112.92(16)
C(3)-C(8)-S(1)	108.11(15)
C(11)-C(10)-S(2)	107.25(16)
O(4)-C(11)-C(10)	107.64(18)
O(4)-C(11)-C(12)	111.63(18)
C(10)-C(11)-C(12)	105.78(18)
C(13)-C(12)-C(18)	110.20(19)
C(13)-C(12)-C(17)	110.54(18)
C(18)-C(12)-C(17)	110.70(19)
C(13)-C(12)-C(11)	108.59(19)
C(18)-C(12)-C(11)	111.38(18)
C(17)-C(12)-C(11)	105.32(18)
C(14)-C(13)-C(12)	125.3(2)
C(13)-C(14)-C(15)	124.4(2)
C(14)-C(15)-C(16)	113.1(2)
C(17)-C(16)-C(15)	113.8(2)
C(16)-C(17)-C(12)	114.37(19)
C(16)-C(17)-S(2)	112.71(17)
C(12)-C(17)-S(2)	108.34(15)

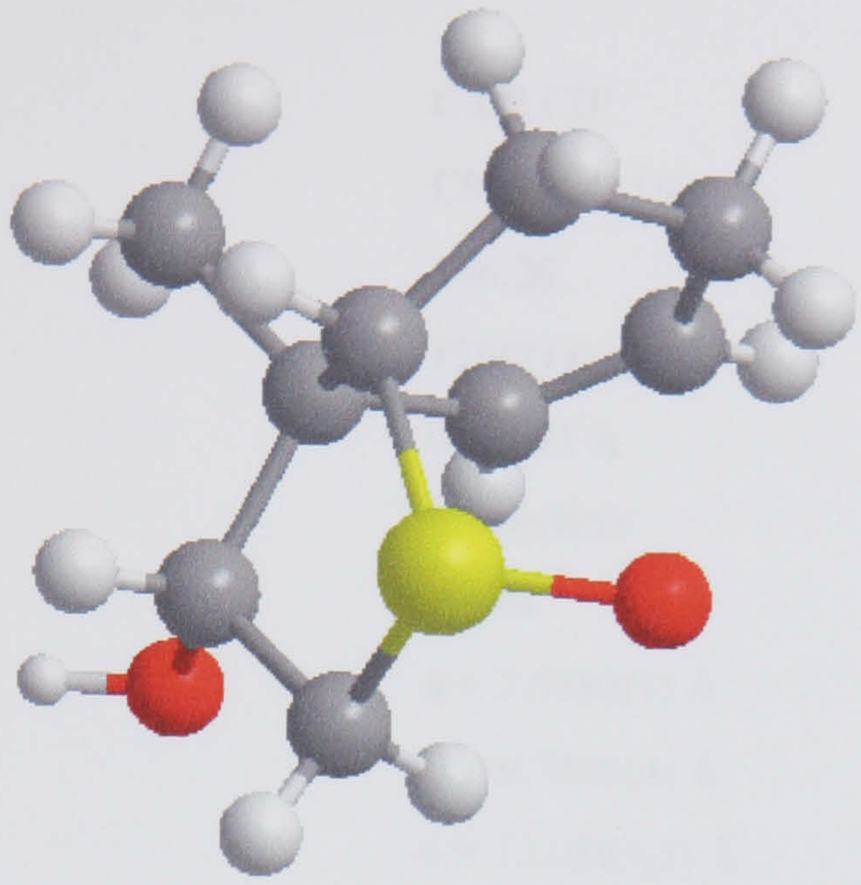
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **91a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	30(1)	20(1)	20(1)	8(1)	12(1)	10(1)
O(1)	47(1)	34(1)	28(1)	20(1)	24(1)	18(1)
C(1)	19(1)	19(1)	30(2)	12(1)	7(1)	7(1)
S(2)	25(1)	20(1)	22(1)	7(1)	10(1)	10(1)
O(2)	31(1)	19(1)	23(1)	12(1)	13(1)	10(1)
C(2)	21(1)	18(1)	19(1)	9(1)	4(1)	5(1)
O(3)	31(1)	31(1)	24(1)	11(1)	17(1)	11(1)
C(3)	19(1)	17(1)	13(1)	5(1)	5(1)	5(1)
O(4)	20(1)	23(1)	22(1)	13(1)	12(1)	10(1)
C(4)	17(1)	16(1)	16(1)	2(1)	3(1)	4(1)
O(5)	33(1)	25(1)	21(1)	11(1)	8(1)	15(1)
C(5)	18(1)	18(1)	28(2)	7(1)	8(1)	7(1)
C(6)	26(2)	26(1)	31(2)	16(1)	8(1)	12(1)
C(7)	23(1)	25(1)	22(2)	9(1)	0(1)	9(1)
C(8)	17(1)	19(1)	17(1)	6(1)	4(1)	2(1)
C(9)	23(1)	23(1)	25(2)	9(1)	9(1)	8(1)
C(10)	15(1)	29(1)	19(1)	11(1)	3(1)	8(1)
C(11)	15(1)	19(1)	19(1)	9(1)	5(1)	5(1)
C(12)	12(1)	19(1)	17(1)	8(1)	2(1)	5(1)
C(13)	18(1)	18(1)	18(1)	4(1)	2(1)	6(1)
C(14)	18(1)	19(1)	30(2)	10(1)	2(1)	6(1)
C(15)	34(2)	29(2)	24(2)	17(1)	1(1)	7(1)
C(16)	32(2)	30(2)	18(1)	9(1)	-5(1)	4(1)
C(17)	16(1)	21(1)	20(1)	9(1)	0(1)	0(1)
C(18)	17(1)	31(2)	32(2)	18(1)	6(1)	9(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **91a**.

	x	y	z	U(eq)
H(1A)	-10677	2269	-240	26
H(1B)	-10793	3757	-125	26
H(2)	-7384	4475	-1458	26
H(2A)	-9318	2628	-1713	22
H(51)	-5950(40)	4200(30)	-3130(20)	50(10)
H(4)	-605	3586	-7171	23
H(4A)	-8611	516	-1725	21
H(5)	-8440	-622	-661	25
H(6A)	-6063	237	801	30
H(6B)	-7812	931	1200	30
H(7A)	-5304	2656	1676	27
H(7B)	-4283	2066	641	27
H(8)	-5268	3834	462	22
H(9A)	-5860	2181	-2215	34
H(9B)	-4412	2068	-1329	34
H(9C)	-4765	3479	-1287	34
H(10A)	-5069	1931	-6227	24
H(10B)	-4825	3282	-6475	24
H(11)	-2606	1824	-7302	20
H(13)	-2471	123	-6530	22
H(14)	-3140	-471	-5148	26
H(15A)	-1576	921	-3477	33
H(15B)	-3456	1462	-3639	33
H(16A)	-1216	3337	-3131	32
H(16B)	412	2628	-3702	32
H(17)	-226	3936	-4618	23
H(18A)	1612	1960	-5512	36
H(18B)	1495	3048	-6049	36
H(18C)	933	1519	-6746	36
H(52)	-7020(50)	5170(30)	-2840(20)	54(11)

6.2 X-ray analysis of 91b



91b

Crystal data for **91b**: $C_9H_{14}O_2S$, M = 186.26, 0.20 0.15 0.10 mm^3, monoclinic, space group $P2_1/n$ (No. 14), a = 7.5780(3), b = 9.7836(4), c = 12.0885(5) Å, β = 92.028(2)°, V = 895.68(6) Å^3, Z = 4, D_c = 1.381 g/cm^3, F_{000} = 400, Nonis KappaCCD CCD diffractometer, MoK radiation, = 0.71073 Å, T = 120(2)K, $2\theta_{max}$ = 54.9°, 2782 reflections collected, 1640 unique (R_{int} = 0.0388). The structure was solved and refined using the programs SHELXS-97 (Sheldrick, 1990) and SHELXL-97 (Sheldrick, 1997) respectively. The program X-Seed (Barbour, 1999) was used as an interface to the SHELX programs, and to prepare the figures. Final *GooF* = 1.069, *R1* = 0.0361, *wR2* = 0.0779, *R* indices based on 1265 reflections with I >2sigma(I) (refinement on F^2), 115 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.317 mm^{-1}.

Table 1. Crystal data and structure refinement for **91b**.

Identification code	C:bB.CIF	
Empirical formula	C9 H14 O2 S	
Formula weight	186.26	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/n	
Unit cell dimensions	a = 7.5780(3) Å	α= 90°.
	b = 9.7836(4) Å	ß= 92.028(2)°.
	c = 12.0885(5) Å	γ= 90°.
Volume	895.68(6) $Å^3$	
Z	4	
Density (calculated)	1.381 Mg/m^3	
Absorption coefficient	0.317 mm^{-1}	
F(000)	400	
Crystal size	0.20 x 0.15 x 0.10 mm^3	
Theta range for data collection	3.12 to 27.46°.	
Index ranges	-9<=h<=9, -12<=k<=12, -14<=l<=14	
Reflections collected	2782	
Independent reflections	1640 [R(int) = 0.0388]	
Completeness to theta = 27.46°	79.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9690 and 0.9394	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1640 / 0 / 115	
Goodness-of-fit on F^2	1.069	
Final R indices [I>2sigma(I)]	R1 = 0.0361, wR2 = 0.0779	
R indices (all data)	R1 = 0.0560, wR2 = 0.0839	
Extinction coefficient	0.010(3)	
Largest diff. peak and hole	0.262 and -0.281 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **91b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	-155(1)	3499(1)	4180(1)	19(1)
O(1)	376(2)	2805(1)	5258(1)	22(1)
C(1)	-2144(3)	2651(2)	3660(2)	20(1)
O(2)	-3104(2)	1191(2)	2147(1)	24(1)
C(2)	-1845(2)	2208(2)	2469(2)	17(1)
C(3)	71(2)	1692(2)	2447(1)	15(1)
C(4)	262(3)	349(2)	3050(1)	17(1)
C(5)	1554(3)	61(2)	3780(2)	20(1)
C(6)	2996(3)	1022(2)	4126(2)	24(1)
C(7)	2988(3)	2345(2)	3455(2)	23(1)
C(8)	1153(2)	2799(2)	3047(2)	16(1)
C(9)	620(3)	1525(2)	1239(2)	24(1)

Table 3. Bond lengths [Å] and angles [°] for **91b**.

S(1)-O(1)	1.5119(13)
S(1)-C(1)	1.813(2)
S(1)-C(8)	1.8497(19)
C(1)-C(2)	1.529(3)
O(2)-C(2)	1.423(2)
C(2)-C(3)	1.538(3)
C(3)-C(4)	1.506(3)
C(3)-C(8)	1.526(3)
C(3)-C(9)	1.541(2)
C(4)-C(5)	1.325(3)
C(5)-C(6)	1.490(3)
C(6)-C(7)	1.527(3)
C(7)-C(8)	1.525(3)
O(1)-S(1)-C(1)	106.61(8)
O(1)-S(1)-C(8)	109.80(8)
C(1)-S(1)-C(8)	92.00(8)
C(2)-C(1)-S(1)	107.88(13)
O(2)-C(2)-C(1)	109.60(16)
O(2)-C(2)-C(3)	112.94(16)
C(1)-C(2)-C(3)	106.28(15)
C(4)-C(3)-C(8)	110.40(15)
C(4)-C(3)-C(2)	110.69(16)
C(8)-C(3)-C(2)	104.50(15)
C(4)-C(3)-C(9)	109.93(15)
C(8)-C(3)-C(9)	111.49(16)
C(2)-C(3)-C(9)	109.73(15)
C(5)-C(4)-C(3)	124.36(18)
C(4)-C(5)-C(6)	124.68(19)
C(5)-C(6)-C(7)	113.41(16)
C(8)-C(7)-C(6)	113.90(17)
C(7)-C(8)-C(3)	114.53(16)
C(7)-C(8)-S(1)	112.00(13)
C(3)-C(8)-S(1)	108.74(13)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **91b**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	23(1)	17(1)	16(1)	-2(1)	-5(1)	2(1)
O(1)	27(1)	23(1)	14(1)	1(1)	-8(1)	3(1)
C(1)	15(1)	28(1)	18(1)	-2(1)	-3(1)	4(1)
O(2)	20(1)	32(1)	18(1)	2(1)	-9(1)	-7(1)
C(2)	17(1)	19(1)	13(1)	1(1)	-4(1)	-1(1)
C(3)	14(1)	19(1)	12(1)	0(1)	-1(1)	0(1)
C(4)	20(1)	15(1)	16(1)	-4(1)	1(1)	-1(1)
C(5)	26(1)	15(1)	19(1)	2(1)	2(1)	5(1)
C(6)	18(1)	27(1)	27(1)	-2(1)	-5(1)	8(1)
C(7)	16(1)	26(1)	26(1)	-1(1)	-1(1)	-4(1)
C(8)	16(1)	19(1)	14(1)	4(1)	-1(1)	-1(1)
C(9)	24(1)	30(1)	17(1)	-1(1)	3(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **91b**.

	x	y	z	U(eq)
H(1A)	-2396	1844	4123	24
H(1B)	-3162	3283	3682	24
H(2)	-1986	3016	1967	20
H(4)	-600	-336	2895	20
H(5)	1560	-822	4107	24
H(6A)	4146	559	4047	29
H(6B)	2880	1250	4918	29
H(7A)	3523	3080	3919	27
H(7B)	3736	2218	2808	27
H(8)	1319	3557	2505	20
H(9A)	1856	1231	1229	35
H(9B)	486	2400	852	35
H(9C)	-132	837	869	35
H(1)	-3550(30)	1460(20)	1490(20)	47(8)

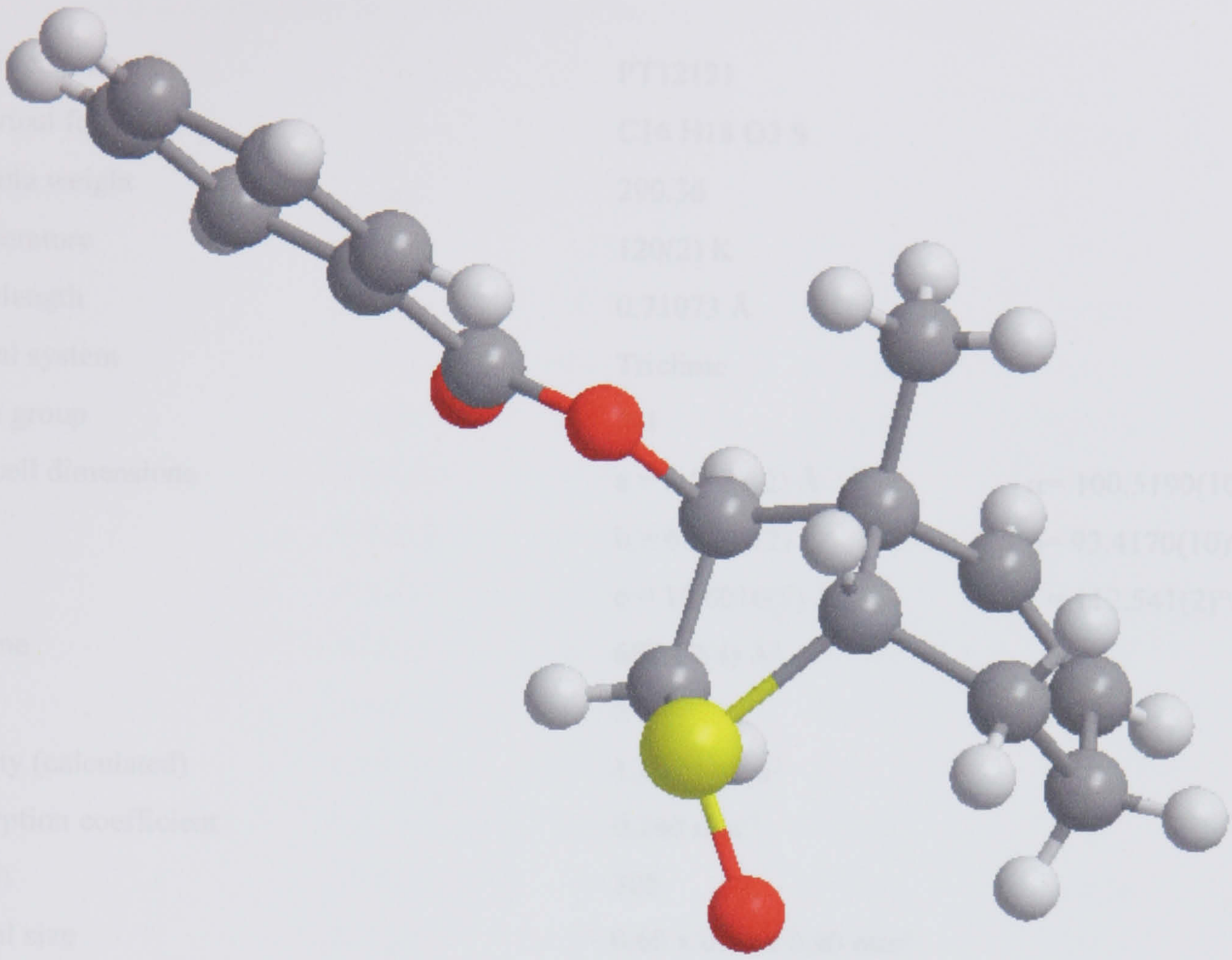
Table 6. Hydrogen bonds for **91b** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(1)...O(1)#1	0.90(2)	1.82(2)	2.7059(19)	172(2)

Symmetry transformations used to generate equivalent atoms:

#1 x-1/2,-y+1/2,z-1/2

6.3 X-ray analysis of 95a



95a

Crystal data for **95a**: $C_{16}H_{18}O_3S$, M = 290.36, 0.60 0.50 0.40 mm^3, triclinic, space group P-1 (No. 2), a = 6.5153(2), b = 6.9845(2), c = 16.8016(5) Å, α = 100.5190(10), β = 93.4170(10), γ = 112.541(2)°, V = 687.19(4) Å^3, Z = 2, D_c = 1.403 g/cm^3, F_{000} = 308, Nonius KappaCCD, MoK radiation, = 0.71073 Å, T = 120(2)K, $2\theta_{max}$ = 54.9°, 4399 reflections collected, 3002 unique (R_{int} = 0.0332). The structure was solved and refined using the programs SHELXS-97 (Sheldrick, 1990) and SHELXL-97 (Sheldrick, 1997) respectively. The program X-Seed (Barbour, 1999) was used as an interface to the SHELX programs, and to prepare the figures. Final *GooF* = 1.026, *R1* = 0.0319, *wR2* = 0.0801, *R* indices based on 2751 reflections with I >2sigma(I) (refinement on F^2), 183 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.240 mm^{-1}.

Table 1. Crystal data and structure refinement for **95a**.

Identification code	PT12121	
Empirical formula	C16 H18 O3 S	
Formula weight	290.36	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.5153(2) Å	α= 100.5190(10)°.
	b = 6.9845(2) Å	β= 93.4170(10)°.
	c = 16.8016(5) Å	γ = 112.541(2)°.
Volume	687.19(4) $Å^3$	
Z	2	
Density (calculated)	1.403 Mg/m^3	
Absorption coefficient	0.240 mm^{-1}	
F(000)	308	
Crystal size	0.60 x 0.50 x 0.40 mm^3	
Theta range for data collection	3.65 to 27.47°.	
Index ranges	-7<=h<=8, -9<=k<=8, -19<=l<=21	
Reflections collected	4399	
Independent reflections	3002 [R(int) = 0.0332]	
Completeness to theta = 27.47°	95.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9101 and 0.8694	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3002 / 0 / 183	
Goodness-of-fit on F^2	1.026	
Final R indices [I>2sigma(I)]	R1 = 0.0319, wR2 = 0.0801	
R indices (all data)	R1 = 0.0358, wR2 = 0.0824	
Extinction coefficient	0.035(9)	
Largest diff. peak and hole	0.325 and -0.364 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **95a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	6806(1)	6269(1)	2198(1)	15(1)
O(1)	6014(2)	4193(1)	1583(1)	22(1)
O(2)	7165(2)	10641(1)	3068(1)	16(1)
O(3)	4104(2)	11326(2)	3284(1)	25(1)
C(1)	9094(2)	8363(2)	1842(1)	14(1)
C(2)	9900(2)	7415(2)	1093(1)	17(1)
C(3)	8277(2)	6737(2)	299(1)	20(1)
C(4)	7341(2)	8353(2)	214(1)	18(1)
C(5)	7386(2)	9853(2)	836(1)	16(1)
C(6)	8307(2)	10134(2)	1720(1)	13(1)
C(7)	6307(2)	9882(2)	2198(1)	14(1)
C(8)	4865(2)	7515(2)	2040(1)	15(1)
C(9)	10244(2)	12330(2)	2014(1)	18(1)
C(10)	5870(2)	11321(2)	3544(1)	16(1)
C(11)	6868(2)	12037(2)	4423(1)	14(1)
C(12)	8910(2)	11977(2)	4694(1)	16(1)
C(13)	9747(2)	12651(2)	5523(1)	19(1)
C(14)	8587(2)	13417(2)	6075(1)	20(1)
C(15)	6572(2)	13500(2)	5805(1)	20(1)
C(16)	5705(2)	12796(2)	4979(1)	17(1)

Table 3. Bond lengths [Å] and angles [°] for **95a**.

S(1)-O(1)	1.5011(9)
S(1)-C(8)	1.8205(12)
S(1)-C(1)	1.8637(13)
O(2)-C(10)	1.3510(15)
O(2)-C(7)	1.4564(14)
O(3)-C(10)	1.2079(16)
C(1)-C(2)	1.5305(17)
C(1)-C(6)	1.5496(16)
C(2)-C(3)	1.5288(18)
C(3)-C(4)	1.4979(18)
C(4)-C(5)	1.3282(18)
C(5)-C(6)	1.5163(17)
C(6)-C(9)	1.5347(16)
C(6)-C(7)	1.5418(17)
C(7)-C(8)	1.5183(17)
C(10)-C(11)	1.4898(17)
C(11)-C(16)	1.3933(17)
C(11)-C(12)	1.3992(18)
C(12)-C(13)	1.3893(18)
C(13)-C(14)	1.3894(19)
C(14)-C(15)	1.3895(19)
C(15)-C(16)	1.3891(18)
O(1)-S(1)-C(8)	108.29(6)
O(1)-S(1)-C(1)	110.12(6)
C(8)-S(1)-C(1)	91.63(6)
C(10)-O(2)-C(7)	115.96(9)
C(2)-C(1)-C(6)	114.42(10)
C(2)-C(1)-S(1)	111.53(8)
C(6)-C(1)-S(1)	108.97(8)
C(3)-C(2)-C(1)	114.12(10)
C(4)-C(3)-C(2)	111.89(10)
C(5)-C(4)-C(3)	123.47(12)
C(4)-C(5)-C(6)	125.53(11)

C(5)-C(6)-C(9)	109.62(10)
C(5)-C(6)-C(7)	105.43(10)
C(9)-C(6)-C(7)	112.27(10)
C(5)-C(6)-C(1)	112.32(10)
C(9)-C(6)-C(1)	110.38(10)
C(7)-C(6)-C(1)	106.74(10)
O(2)-C(7)-C(8)	108.13(10)
O(2)-C(7)-C(6)	108.50(9)
C(8)-C(7)-C(6)	106.63(10)
C(7)-C(8)-S(1)	105.55(8)
O(3)-C(10)-O(2)	123.60(12)
O(3)-C(10)-C(11)	124.37(12)
O(2)-C(10)-C(11)	112.03(10)
C(16)-C(11)-C(12)	120.09(12)
C(16)-C(11)-C(10)	117.78(11)
C(12)-C(11)-C(10)	122.13(11)
C(13)-C(12)-C(11)	119.45(12)
C(12)-C(13)-C(14)	120.25(12)
C(13)-C(14)-C(15)	120.34(12)
C(16)-C(15)-C(14)	119.76(12)
C(15)-C(16)-C(11)	120.09(12)

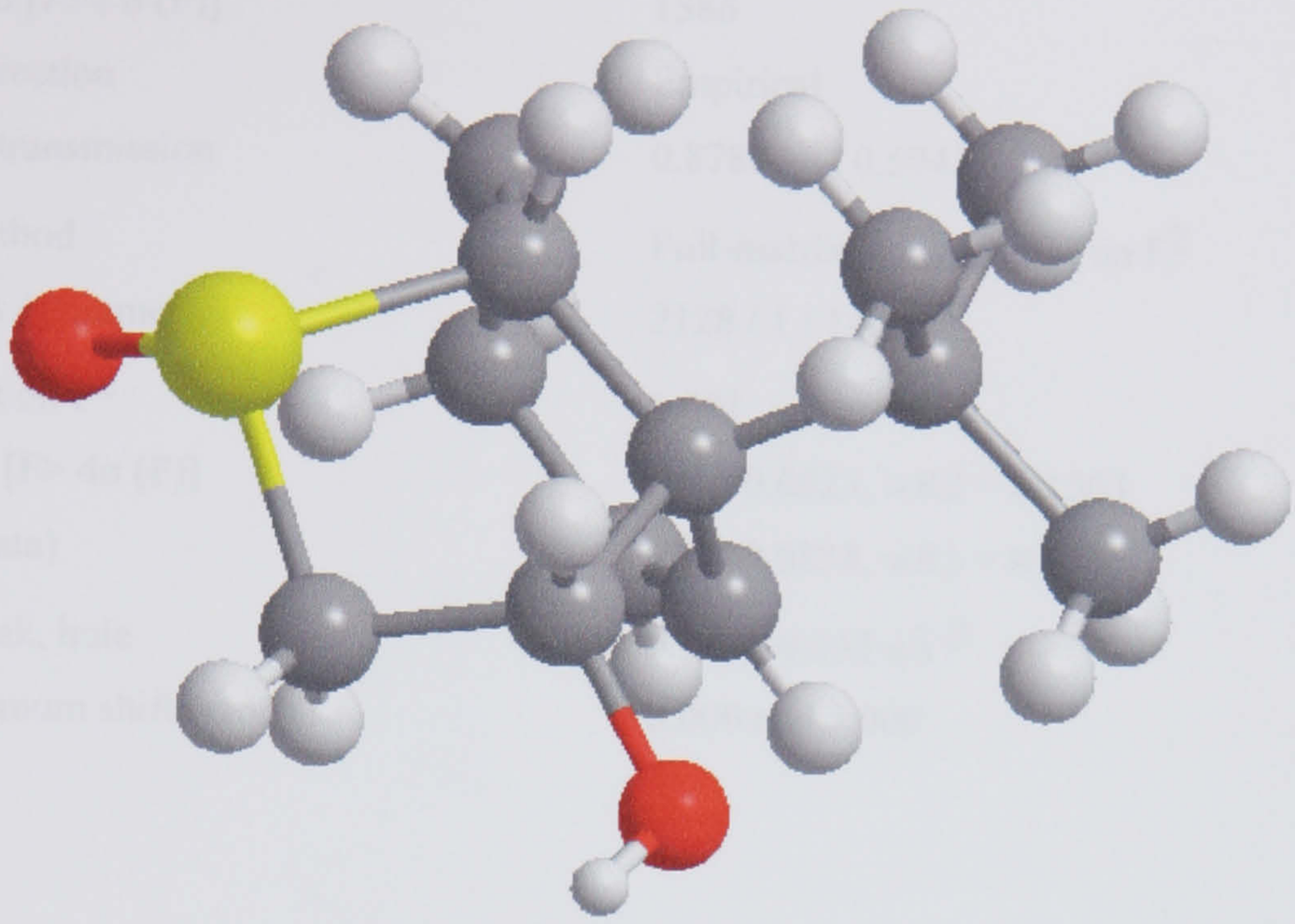
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **95a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	15(1)	15(1)	16(1)	4(1)	2(1)	7(1)
O(1)	23(1)	12(1)	27(1)	1(1)	5(1)	6(1)
O(2)	17(1)	21(1)	12(1)	-1(1)	1(1)	11(1)
O(3)	21(1)	38(1)	20(1)	2(1)	2(1)	19(1)
C(1)	11(1)	13(1)	17(1)	2(1)	-1(1)	5(1)
C(2)	15(1)	18(1)	22(1)	4(1)	5(1)	10(1)
C(3)	24(1)	18(1)	17(1)	1(1)	5(1)	10(1)
C(4)	15(1)	21(1)	15(1)	4(1)	1(1)	6(1)
C(5)	14(1)	19(1)	17(1)	6(1)	2(1)	9(1)
C(6)	12(1)	12(1)	15(1)	1(1)	1(1)	6(1)
C(7)	13(1)	17(1)	13(1)	0(1)	0(1)	7(1)
C(8)	12(1)	18(1)	17(1)	3(1)	3(1)	7(1)
C(9)	17(1)	14(1)	21(1)	2(1)	2(1)	5(1)
C(10)	16(1)	13(1)	18(1)	3(1)	4(1)	7(1)
C(11)	15(1)	11(1)	16(1)	3(1)	4(1)	4(1)
C(12)	17(1)	14(1)	18(1)	2(1)	4(1)	7(1)
C(13)	18(1)	18(1)	20(1)	3(1)	0(1)	7(1)
C(14)	24(1)	17(1)	15(1)	1(1)	3(1)	6(1)
C(15)	23(1)	19(1)	19(1)	2(1)	8(1)	10(1)
C(16)	17(1)	16(1)	20(1)	4(1)	5(1)	8(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **95a**.

	x	y	z	U(eq)
H(1)	10393	9016	2293	17
H(2A)	11364	8478	1020	21
H(2B)	10143	6162	1196	21
H(3A)	9073	6531	-172	24
H(3B)	7028	5360	290	24
H(4)	6679	8303	-313	21
H(5)	6792	10834	718	19
H(7)	5431	10670	2020	17
H(8A)	4063	6980	1473	18
H(8B)	3746	7216	2424	18
H(9A)	11455	12435	1683	27
H(9B)	10811	12522	2589	27
H(9C)	9704	13436	1958	27
H(12)	9718	11478	4315	20
H(13)	11118	12588	5713	23
H(14)	9175	13887	6640	24
H(15)	5789	14037	6183	24
H(16)	4316	12832	4794	21

6.4 X-ray analysis of 118a



118a

Table 1. Crystal data and structure refinement for **118a**.

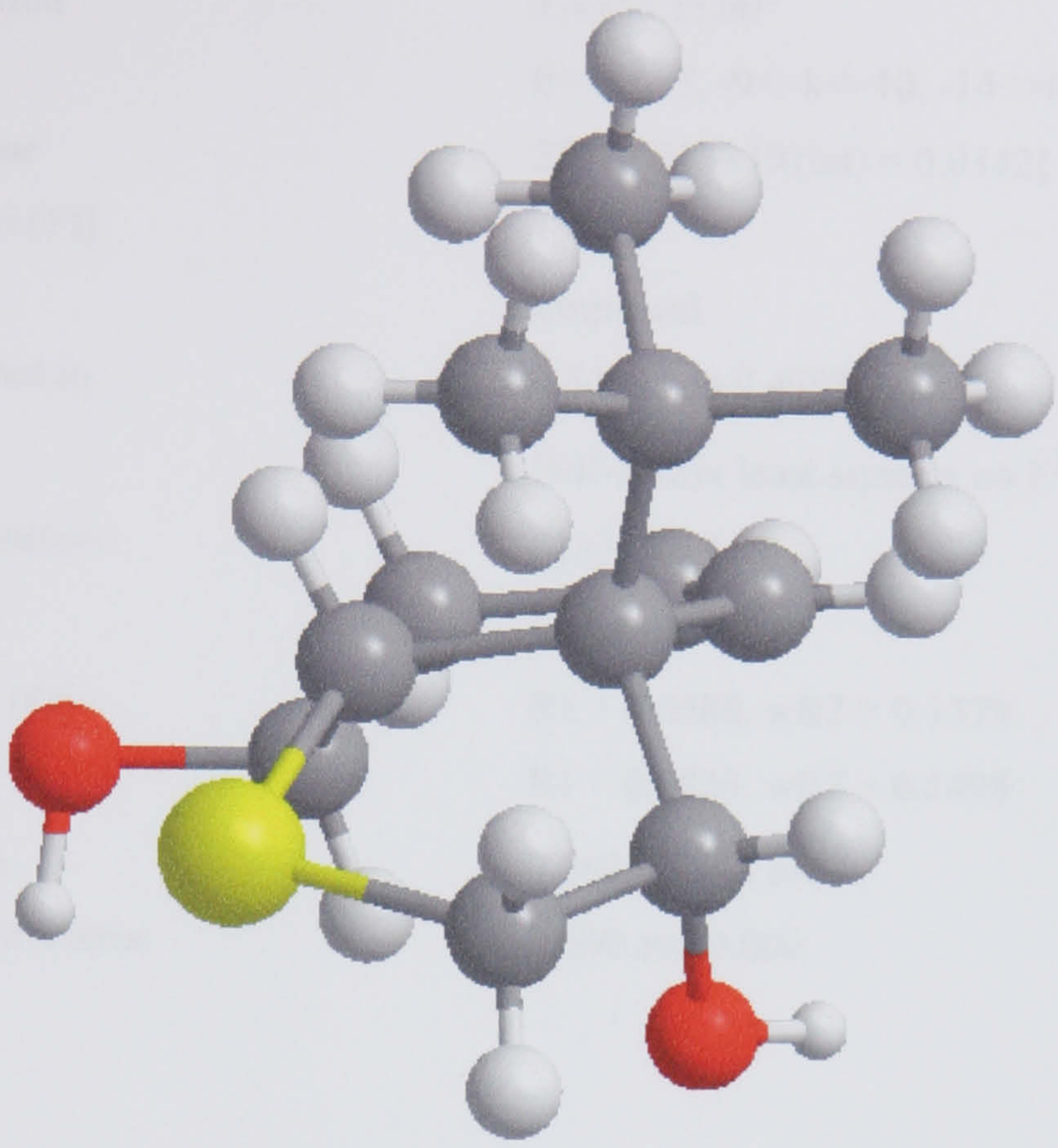
Identification code	RG0401b	
Empirical formula	C12 H20 O2 S	
Formula weight	228.34	
Temperature	203(2) K	
Diffractometer, wavelength	Bruker P4, 0.71073 Å	
Crystal system, space group	Monoclinic, P2(1)/n	
Unit cell dimensions	a = 6.262(4) Å	α = 90°
	b = 23.647(6) Å	ß = 107.26(4)°
	c = 8.550(4) Å	γ= 90°
Volume, Z	1209.0(10) $Å^3$, 4	
Density (calculated)	1.254 Mg/m^3	
Absorption coefficient	0.247 mm^{-1}	
F(000)	496	
Crystal colour / morphology	Colourless blocks	
Crystal size	0.97 x 0.38 x 0.23 mm^3	
θ range for data collection	2.64 to 24.99°	
Index ranges	0<=h<=7, 0<=k<=28, -10<=l<=9	

Reflns collected / unique	2326 / 2128 [R(int) = 0.0210]
Reflns observed [F>4 σ (F)]	1586
Absorption correction	Empirical
Max. and min. transmission	0.8780 and 0.5941
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2128 / 1 / 140
Goodness-of-fit on F^2	1.081
Final R indices [F> 4σ (F)]	R1 = 0.0623, wR2 = 0.1563
R indices (all data)	R1 = 0.0858, wR2 = 0.1686
Largest diff. peak, hole	0.703, -0.555 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.000

Table 2. Bond lengths [Å] and angles [°] for **118a**.

S(1)-O(1)	1.511(3)
S(1)-C(9)	1.789(6)
S(1)-C(2)	1.857(4)
C(2)-C(3)	1.543(5)
C(2)-C(7)	1.552(4)
C(3)-C(4)	1.521(6)
C(4)-C(5)	1.471(5)
C(5)-C(6)	1.323(5)
C(6)-C(7)	1.506(4)
C(7)-C(8)	1.550(4)
C(7)-C(10)	1.591(4)
C(8)-O(14)	1.402(4)
C(8)-C(9)	1.535(5)
C(10)-C(13)	1.530(4)
C(10)-C(11)	1.534(4)
C(10)-C(12)	1.540(4)
O(1)-S(1)-C(9)	107.1(2)
O(1)-S(1)-C(2)	109.4(2)
C(9)-S(1)-C(2)	92.09(16)
C(3)-C(2)-C(7)	116.4(3)
C(3)-C(2)-S(1)	109.5(2)
C(7)-C(2)-S(1)	108.7(2)
C(4)-C(3)-C(2)	113.3(3)
C(5)-C(4)-C(3)	112.8(3)
C(6)-C(5)-C(4)	124.7(3)
C(5)-C(6)-C(7)	126.0(3)
C(6)-C(7)-C(8)	107.3(2)
C(6)-C(7)-C(2)	110.7(2)
C(8)-C(7)-C(2)	104.7(3)
C(6)-C(7)-C(10)	110.9(2)
C(8)-C(7)-C(10)	111.3(2)
C(2)-C(7)-C(10)	111.5(2)
O(14)-C(8)-C(9)	112.5(3)
O(14)-C(8)-C(7)	112.5(3)
C(9)-C(8)-C(7)	105.5(3)
C(8)-C(9)-S(1)	103.3(3)
C(13)-C(10)-C(11)	108.6(3)
C(13)-C(10)-C(12)	107.6(3)
C(11)-C(10)-C(12)	107.5(3)
C(13)-C(10)-C(7)	111.8(3)
C(11)-C(10)-C(7)	110.0(2)
C(12)-C(10)-C(7)	111.2(2)

6.5 X-ray analysis of 118b



118b

Table 1. Crystal data and structure refinement for **118b**.

Identification code	RG0402	
Empirical formula	C12 H20 O2 S	
Formula weight	228.34	
Temperature	293(2) K	
Diffractometer, wavelength	Bruker P4, 0.71073 Å	
Crystal system, space group	Triclinic, P-1	
Unit cell dimensions	a = 6.230(2) Å	α = 75.617(11)°
	b = 8.6816(15) Å	ß = 77.44(2)°
	c = 12.315(2) Å	γ= 74.08(3)°
Volume, Z	612.4(3) $Å^3$, 2	
Density (calculated)	1.238 Mg/m^3	
Absorption coefficient	0.244 mm^{-1}	
F(000)	248	
Crystal colour / morphology	Colourless blocks	

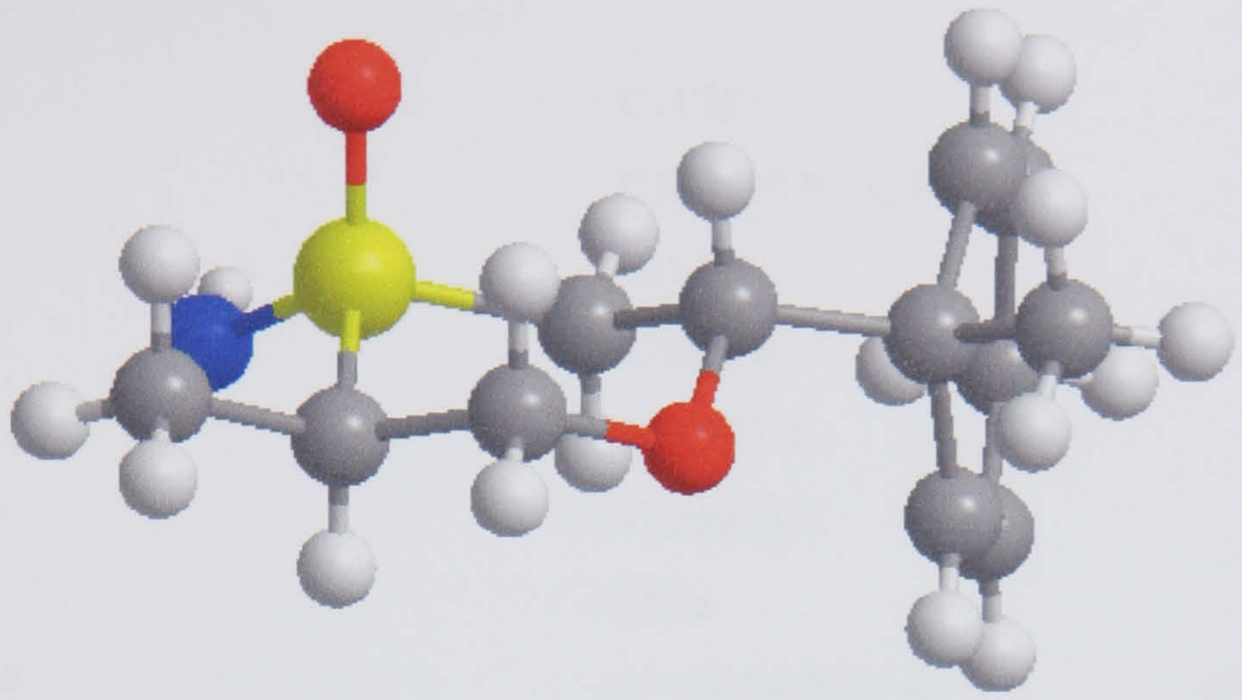
Crystal size	0.60 x 0.40 x 0.13 mm^3
θ range for data collection	2.49 to 25.00°
Index ranges	0<=h<=7, -9<=k<=10, -14<=l<=14
Reflns collected / unique	2347 / 2133 [R(int) = 0.0342]
Reflns observed [F>4 σ (F)]	1594
Absorption correction	Empirical
Max. and min. transmission	0.8408 and 0.4998

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2133 / 2 / 144
Goodness-of-fit on F^2	1.024
Final R indices [F>4 σ (F)]	R1 = 0.0588, wR2 = 0.1379
R indices (all data)	R1 = 0.0823, wR2 = 0.1498
Largest diff. peak, hole	0.262, -0.318 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.000

Table 2. Bond lengths [Å] and angles [°] for **118b**.

S(1)-C(2)	1.817(4)
S(1)-C(9)	1.837(3)
C(2)-C(3)	1.516(4)
C(3)-O(10)	1.425(4)
C(3)-C(4)	1.564(4)
C(4)-C(5)	1.514(4)
C(4)-C(9)	1.562(4)
C(4)-C(11)	1.593(4)
C(5)-C(6)	1.325(5)
C(6)-C(7)	1.496(5)
C(7)-C(8)	1.518(4)
C(8)-O(15)	1.429(3)
C(8)-C(9)	1.535(4)
C(11)-C(14)	1.534(5)
C(11)-C(12)	1.541(6)
C(11)-C(13)	1.544(5)
C(2)-S(1)-C(9)	94.61(14)
C(3)-C(2)-S(1)	107.0(2)
O(10)-C(3)-C(2)	105.1(3)
O(10)-C(3)-C(4)	110.4(2)
C(2)-C(3)-C(4)	109.2(2)
C(5)-C(4)-C(9)	111.0(2)
C(5)-C(4)-C(3)	107.8(2)
C(9)-C(4)-C(3)	104.7(2)
C(5)-C(4)-C(11)	108.0(2)
C(9)-C(4)-C(11)	111.5(2)
C(3)-C(4)-C(11)	113.7(2)
C(6)-C(5)-C(4)	125.4(3)
C(5)-C(6)-C(7)	122.7(3)
C(6)-C(7)-C(8)	110.0(3)
O(15)-C(8)-C(7)	109.1(2)
O(15)-C(8)-C(9)	109.3(2)
C(7)-C(8)-C(9)	110.0(2)
C(8)-C(9)-C(4)	115.1(2)
C(8)-C(9)-S(1)	108.92(18)
C(4)-C(9)-S(1)	108.31(17)
C(14)-C(11)-C(12)	106.9(4)
C(14)-C(11)-C(13)	107.2(3)
C(12)-C(11)-C(13)	108.1(4)
C(14)-C(11)-C(4)	109.3(3)
C(12)-C(11)-C(4)	114.4(3)
C(13)-C(11)-C(4)	110.6(3)

6.6 X-ray analysis of 170



170

Crystal data for **170**: $C_{12}H_{19}NO_2S$, $M = 241.34$, colourless prism, 0.40 0.35 0.20 mm^3, tetragonal, space group $I4_1/a$ (No. 88), $a = b = 20.9699(9)$, $c = 11.2756(6)$ Å, $V = 4958.3(4)$ $Å^3$, $Z = 16$, $D_c = 1.293$ g/cm^3, $F_{000} = 2080$, Nonius KappaCCD, MoK radiation, = 0.71073 Å, $T = 120(2)$K, $2\theta_{max} = 54.8°$, 3252 reflections collected, 2136 unique ($R_{int} = 0.0345$). Final *GooF* = 1.003, *R1* = 0.0434, *wR2* = 0.0804, *R* indices based on 1417 reflections with I >2sigma(I) (refinement on F^2), 152 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.247$ mm^{-1}.

Table 1. Crystal data and structure refinement for **170**.

Identification code	C:.CIF	
Empirical formula	C12 H19 N O2 S	
Formula weight	241.34	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	I41/a	
Unit cell dimensions	a = 20.9699(9) Å	α= 90°.
	b = 20.9699(9) Å	ß= 90°.
	c = 11.2756(6) Å	γ= 90°.
Volume	4958.3(4) Å^3	
Z	16	
Density (calculated)	1.293 Mg/m^3	
Absorption coefficient	0.247 mm^{-1}	
F(000)	2080	
Crystal size	0.40 x 0.35 x 0.20 mm^3	
Theta range for data collection	2.75 to 27.40°.	
Index ranges	-26<=h<=26, -18<=k<=18, -14<=l<=10	
Reflections collected	3252	
Independent reflections	2136 [R(int) = 0.0345]	
Completeness to theta = 27.40°	75.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9522 and 0.9075	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2136 / 0 / 152	
Goodness-of-fit on F^2	1.003	
Final R indices [I>2sigma(I)]	R1 = 0.0434, wR2 = 0.0804	
R indices (all data)	R1 = 0.0866, wR2 = 0.0930	
Extinction coefficient	0.0014(2)	
Largest diff. peak and hole	0.256 and -0.259 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **170**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	7849(1)	3809(1)	1340(1)	21(1)
O(1)	8978(1)	2987(1)	2181(1)	25(1)
N(1)	7724(1)	4488(1)	922(2)	25(1)
O(2)	7341(1)	3333(1)	1337(1)	25(1)
C(2)	8478(1)	3114(1)	3014(2)	22(1)
C(3)	8203(1)	3772(1)	2764(2)	21(1)
C(5)	8485(1)	3516(1)	437(2)	21(1)
C(6)	8747(1)	2906(1)	1004(2)	27(1)
C(7)	8245(1)	3399(1)	-820(2)	28(1)
C(8)	8751(1)	3058(1)	4284(2)	20(1)
C(9)	9234(1)	3573(1)	4512(2)	23(1)
C(10)	9150(1)	4053(1)	5251(2)	28(1)
C(11)	8555(1)	4149(1)	5965(2)	37(1)
C(12)	8113(1)	3596(1)	5875(2)	32(1)
C(13)	8194(1)	3117(1)	5137(2)	26(1)
C(14)	9060(1)	2400(1)	4426(2)	30(1)

Table 3. Bond lengths [Å] and angles [°] for **170**.

S(1)-O(2)	1.4594(15)
S(1)-N(1)	1.524(2)
S(1)-C(3)	1.770(2)
S(1)-C(5)	1.787(2)
O(1)-C(6)	1.423(2)
O(1)-C(2)	1.432(2)
C(2)-C(3)	1.522(3)
C(2)-C(8)	1.546(3)
C(5)-C(7)	1.524(3)
C(5)-C(6)	1.531(3)
C(8)-C(9)	1.502(3)
C(8)-C(13)	1.517(3)
C(8)-C(14)	1.533(3)
C(9)-C(10)	1.319(3)
C(10)-C(11)	1.498(3)
C(11)-C(12)	1.488(3)
C(12)-C(13)	1.316(3)
O(2)-S(1)-N(1)	120.91(10)
O(2)-S(1)-C(3)	106.15(10)
N(1)-S(1)-C(3)	113.17(11)
O(2)-S(1)-C(5)	107.95(10)
N(1)-S(1)-C(5)	105.83(12)
C(3)-S(1)-C(5)	100.92(11)
C(6)-O(1)-C(2)	112.65(16)
O(1)-C(2)-C(3)	108.94(18)
O(1)-C(2)-C(8)	108.80(17)
C(3)-C(2)-C(8)	112.37(18)
C(2)-C(3)-S(1)	111.48(15)
C(7)-C(5)-C(6)	111.83(18)
C(7)-C(5)-S(1)	109.82(15)
C(6)-C(5)-S(1)	108.47(15)
O(1)-C(6)-C(5)	114.29(18)
C(9)-C(8)-C(13)	110.61(19)

C(9)-C(8)-C(14)	110.06(19)
C(13)-C(8)-C(14)	109.43(19)
C(9)-C(8)-C(2)	110.71(18)
C(13)-C(8)-C(2)	107.20(18)
C(14)-C(8)-C(2)	108.75(17)
C(10)-C(9)-C(8)	124.5(2)
C(9)-C(10)-C(11)	123.6(2)
C(12)-C(11)-C(10)	112.2(2)
C(13)-C(12)-C(11)	123.9(2)
C(12)-C(13)-C(8)	124.2(2)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **170**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	19(1)	21(1)	24(1)	0(1)	1(1)	0(1)
O(1)	22(1)	32(1)	20(1)	-3(1)	1(1)	6(1)
N(1)	29(1)	18(1)	29(1)	3(1)	4(1)	6(1)
O(2)	19(1)	24(1)	31(1)	2(1)	-2(1)	-5(1)
C(2)	18(1)	21(1)	26(2)	-3(1)	3(1)	0(1)
C(3)	18(1)	23(2)	23(2)	-1(1)	1(1)	0(1)
C(5)	19(1)	20(1)	25(2)	-2(1)	3(1)	0(1)
C(6)	28(2)	28(2)	25(2)	-4(1)	1(1)	5(1)
C(7)	28(2)	29(2)	26(2)	0(1)	3(1)	0(1)
C(8)	20(1)	19(1)	21(1)	0(1)	-1(1)	-1(1)
C(9)	21(1)	24(2)	25(2)	2(1)	0(1)	-4(1)
C(10)	31(2)	25(2)	28(2)	2(1)	-8(1)	-5(1)
C(11)	45(2)	33(2)	32(2)	-7(1)	-1(2)	3(1)
C(12)	32(2)	40(2)	25(2)	1(1)	8(1)	5(1)
C(13)	24(2)	29(2)	27(2)	9(1)	-1(1)	-2(1)
C(14)	33(2)	27(2)	30(2)	1(1)	-6(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **170**.

	x	y	z	U(eq)
H(2)	8134	2789	2910	26
H(3A)	8546	4094	2818	26
H(3B)	7878	3875	3373	26
H(5)	8832	3843	412	25
H(6A)	8405	2581	1011	32
H(6B)	9098	2742	503	32
H(7A)	8589	3216	-1300	41
H(7B)	8108	3804	-1171	41
H(7C)	7885	3102	-798	41
H(9)	9627	3551	4095	28
H(10)	9485	4355	5335	34
H(11A)	8672	4216	6806	44
H(11B)	8334	4538	5683	44
H(12)	7751	3589	6381	39
H(13)	7884	2787	5138	32
H(14A)	9411	2357	3857	44
H(14B)	8742	2068	4277	44
H(14C)	9226	2356	5234	44
H(1)	7516(11)	4641(11)	1390(20)	24(9)

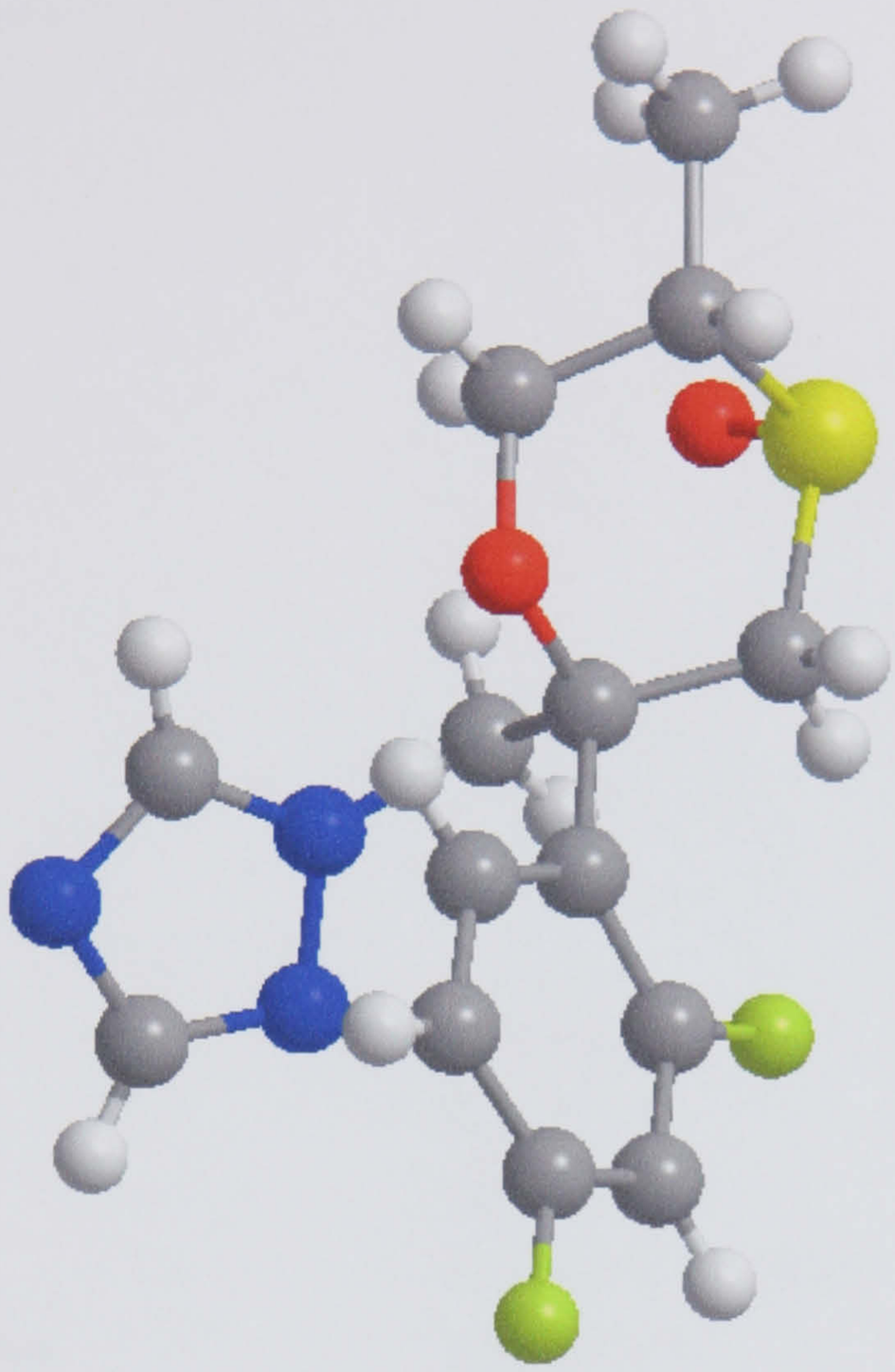
Table 6. Hydrogen bonds for **170** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	(DHA)
N(1)-H(1)...N(1)#1	0.76(2)	2.55(2)	3.2697(15)	157(2)

Symmetry transformations used to generate equivalent atoms:

#1 y+1/4,-x+5/4,z+1/4

6.7 X-ray analysis of 162



162

Crystal data for **162**: $C_{14}H_{15}F_2N_3O_2S$, M = 327.35, colourless block, 0.20 0.15 0.10 mm^3, monoclinic, space group $P2_1/c$ (No. 14), a = 6.7573(3), b = 20.1766(8), c = 10.6727(5) Å, β = 94.572(2)°, V = 1450.48(11) Å^3, Z = 4, D_c = 1.499 g/cm^3, F_{000} = 680, Nonius KappaCCD, MoK radiation, = 0.71073 Å, T = 120(2)K, $2\theta_{max}$ = 54.9°, 5527 reflections collected, 3245 unique (R_{int} = 0.0375). The structure was solved and refined using the programs SHELXS-97 (Sheldrick, 1990) and SHELXL-97 (Sheldrick, 1997) respectively. The program X-Seed (Barbour, 1999) was used as an interface to the SHELX programs, and to prepare the figures. Final *GooF* = 1.010, *R1* = 0.0419, *wR2* = 0.0864, *R* indices based on 2234 reflections with I >2sigma(I) (refinement on F^2), 201 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.256 mm^{-1}.

Table 1. Crystal data and structure refinement for **162**.

Identification code	C:.CIF	
Empirical formula	C14 H15 F2 N3 O2 S	
Formula weight	327.35	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/c	
Unit cell dimensions	a = 6.7573(3) Å	α= 90°.
	b = 20.1766(8) Å	ß= 94.572(2)°.
	c = 10.6727(5) Å	γ= 90°.
Volume	1450.48(11) $Å^3$	
Z	4	
Density (calculated)	1.499 Mg/m^3	
Absorption coefficient	0.256 mm^{-1}	
F(000)	680	
Crystal size	0.20 x 0.15 x 0.10 mm^3	
Theta range for data collection	3.58 to 27.47°.	
Index ranges	-8<=h<=8, -26<=k<=23, -13<=l<=13	
Reflections collected	5527	
Independent reflections	3245 [R(int) = 0.0375]	
Completeness to theta = 27.47°	97.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9748 and 0.9505	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3245 / 0 / 201	
Goodness-of-fit on F^2	1.010	
Final R indices [I>2sigma(I)]	R1 = 0.0419, wR2 = 0.0864	
R indices (all data)	R1 = 0.0786, wR2 = 0.0977	
Extinction coefficient	0.0052(16)	
Largest diff. peak and hole	0.274 and -0.351 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **162**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	3809(1)	3095(1)	9667(1)	22(1)
F(1)	2439(2)	904(1)	10177(1)	32(1)
F(2)	-2652(2)	76(1)	12459(1)	40(1)
O(1)	3577(2)	3093(1)	8248(1)	26(1)
O(2)	-647(2)	2745(1)	10040(1)	22(1)
N(1)	-1527(2)	1709(1)	7995(1)	21(1)
N(2)	-1697(2)	1041(1)	7824(2)	30(1)
N(3)	-4731(2)	1530(1)	7673(2)	29(1)
C(1)	1865(3)	3637(1)	10145(2)	24(1)
C(2)	-116(3)	3380(1)	9571(2)	25(1)
C(3)	590(3)	2190(1)	9786(2)	20(1)
C(4)	2775(3)	2332(1)	10225(2)	21(1)
C(5)	2301(3)	4334(1)	9704(2)	32(1)
C(6)	394(3)	2008(1)	8370(2)	21(1)
C(7)	-3654(3)	968(1)	7635(2)	33(1)
C(8)	-3330(3)	1983(1)	7907(2)	23(1)
C(9)	-238(3)	1623(1)	10541(2)	20(1)
C(10)	680(3)	1009(1)	10694(2)	24(1)
C(11)	-79(3)	486(1)	11325(2)	27(1)
C(12)	-1883(3)	584(1)	11810(2)	27(1)
C(13)	-2925(3)	1165(1)	11682(2)	27(1)
C(14)	-2078(3)	1681(1)	11043(2)	22(1)

Table 3. Bond lengths [Å] and angles [°] for **162**.

S(1)-O(1)	1.5105(13)
S(1)-C(4)	1.8107(19)
S(1)-C(1)	1.8139(19)
F(1)-C(10)	1.365(2)
F(2)-C(12)	1.364(2)
O(2)-C(2)	1.431(2)
O(2)-C(3)	1.436(2)
N(1)-C(8)	1.334(2)
N(1)-N(2)	1.364(2)
N(1)-C(6)	1.457(2)
N(2)-C(7)	1.330(3)
N(3)-C(8)	1.326(2)
N(3)-C(7)	1.349(3)
C(1)-C(2)	1.518(3)
C(1)-C(5)	1.520(3)
C(3)-C(9)	1.531(3)
C(3)-C(4)	1.540(3)
C(3)-C(6)	1.551(2)
C(9)-C(10)	1.389(3)
C(9)-C(14)	1.398(3)
C(10)-C(11)	1.375(3)
C(11)-C(12)	1.376(3)
C(12)-C(13)	1.369(3)
C(13)-C(14)	1.393(3)
O(1)-S(1)-C(4)	108.40(8)
O(1)-S(1)-C(1)	105.30(8)
C(4)-S(1)-C(1)	96.49(9)
C(2)-O(2)-C(3)	117.78(13)
C(8)-N(1)-N(2)	109.46(15)
C(8)-N(1)-C(6)	129.52(16)
N(2)-N(1)-C(6)	120.59(15)
C(7)-N(2)-N(1)	101.59(16)
C(8)-N(3)-C(7)	101.88(16)

C(2)-C(1)-C(5)	112.19(15)
C(2)-C(1)-S(1)	108.40(13)
C(5)-C(1)-S(1)	107.98(13)
O(2)-C(2)-C(1)	113.72(15)
O(2)-C(3)-C(9)	103.92(14)
O(2)-C(3)-C(4)	110.87(15)
C(9)-C(3)-C(4)	111.12(15)
O(2)-C(3)-C(6)	111.26(14)
C(9)-C(3)-C(6)	109.24(15)
C(4)-C(3)-C(6)	110.27(14)
C(3)-C(4)-S(1)	116.34(13)
N(1)-C(6)-C(3)	111.75(14)
N(2)-C(7)-N(3)	115.84(19)
N(3)-C(8)-N(1)	111.23(17)
C(10)-C(9)-C(14)	115.60(17)
C(10)-C(9)-C(3)	123.33(17)
C(14)-C(9)-C(3)	120.89(17)
F(1)-C(10)-C(11)	116.76(17)
F(1)-C(10)-C(9)	119.04(17)
C(11)-C(10)-C(9)	124.20(18)
C(10)-C(11)-C(12)	116.74(19)
F(2)-C(12)-C(13)	118.71(18)
F(2)-C(12)-C(11)	117.86(18)
C(13)-C(12)-C(11)	123.43(18)
C(12)-C(13)-C(14)	117.41(18)
C(13)-C(14)-C(9)	122.58(19)

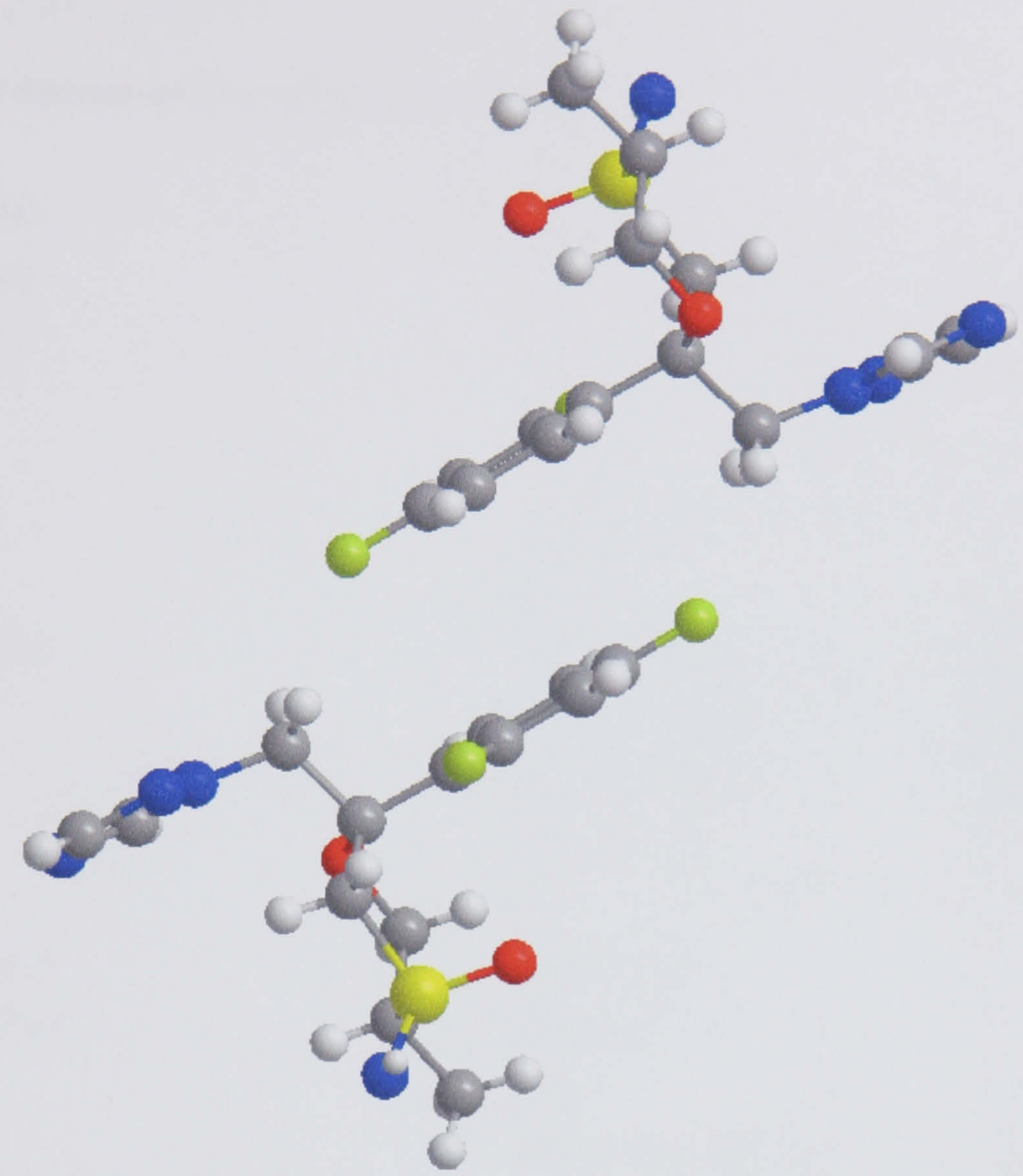
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **162**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	21(1)	27(1)	19(1)	1(1)	3(1)	-1(1)
F(1)	25(1)	31(1)	42(1)	4(1)	13(1)	6(1)
F(2)	43(1)	39(1)	39(1)	11(1)	8(1)	-12(1)
O(1)	29(1)	31(1)	17(1)	1(1)	7(1)	0(1)
O(2)	21(1)	23(1)	22(1)	0(1)	5(1)	4(1)
N(1)	20(1)	25(1)	17(1)	0(1)	1(1)	1(1)
N(2)	30(1)	24(1)	35(1)	-4(1)	-1(1)	-1(1)
N(3)	23(1)	36(1)	28(1)	2(1)	0(1)	-2(1)
C(1)	26(1)	27(1)	19(1)	-2(1)	2(1)	4(1)
C(2)	25(1)	23(1)	25(1)	1(1)	2(1)	4(1)
C(3)	17(1)	25(1)	19(1)	-2(1)	4(1)	3(1)
C(4)	19(1)	26(1)	16(1)	2(1)	3(1)	2(1)
C(5)	34(1)	27(1)	36(1)	-1(1)	4(1)	0(1)
C(6)	18(1)	29(1)	18(1)	1(1)	4(1)	-1(1)
C(7)	30(1)	31(1)	38(1)	-1(1)	-4(1)	-8(1)
C(8)	22(1)	29(1)	17(1)	2(1)	3(1)	2(1)
C(9)	19(1)	25(1)	15(1)	-1(1)	0(1)	-2(1)
C(10)	21(1)	31(1)	21(1)	-2(1)	3(1)	-1(1)
C(11)	30(1)	25(1)	25(1)	-1(1)	-1(1)	0(1)
C(12)	30(1)	32(1)	20(1)	3(1)	1(1)	-9(1)
C(13)	22(1)	40(1)	20(1)	-3(1)	3(1)	-4(1)
C(14)	21(1)	30(1)	17(1)	-3(1)	1(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **162**.

	x	y	z	U(eq)
H(1)	1868	3633	11082	28
H(2A)	-1165	3703	9740	29
H(2B)	-65	3350	8648	29
H(4A)	3590	1958	9955	25
H(4B)	2901	2339	11156	25
H(5A)	2262	4342	8784	48
H(5B)	3621	4471	10058	48
H(5C)	1302	4641	9985	48
H(6A)	561	2413	7865	26
H(6B)	1462	1694	8193	26
H(7)	-4255	548	7482	40
H(8)	-3578	2443	7999	27
H(11)	607	76	11423	32
H(13)	-4179	1214	12017	32
H(14)	-2779	2088	10945	27

6.8 X-ray analysis of 165



165

Crystal data for **165**: $C_{14}H_{16}F_2N_4O_2S$, M = 342.37, colourless block, 0.80 0.70 0.20 mm^3, orthorhombic, space group $Pca2_1$ (No. 29), a = 14.5953(2), b = 7.35510(10), c = 28.7401(4) Å, V = 3085.25(7) Å^3, Z = 8, D_c = 1.474 g/cm^3, F_{000} = 1424, Nonius KappaCCD, MoK radiation, = 0.71073 Å, T = 120(2)K, $2\theta_{max}$ = 55.0°, 6643 reflections collected, 6643 unique (R_{int} = 0.0000). The structure was solved and refined using the programs SHELXS-97 (Sheldrick, 1990) and SHELXL-97 (Sheldrick, 1997) respectively. The program X-Seed (Barbour, 1999) was used as an interface to the SHELX programs, and to prepare the figures. Final *GooF* = 1.142, *R1* = 0.0481, *wR2* = 0.0885, *R* indices based on 5816 reflections with I >2sigma(I) (refinement on F^2), 427 parameters, 1 restraint. Lp and absorption corrections applied, μ = 0.246 mm^{-1}. Absolute

structure parameter = 0.48(8) (Flack, H. D. *Acta Cryst.* **1983**. *A39*, 876-881).

Table 1. Crystal data and structure refinement for **165**.

Identification code	C:A.CIF	
Empirical formula	C14 H16 F2 N4 O2 S	
Formula weight	342.37	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pca21	
Unit cell dimensions	a = 14.5953(2) Å	α = 90°.
	b = 7.35510(10) Å	ß= 90°.
	c = 28.7401(4) Å	γ= 90°.
Volume	3085.25(7) Å^3	
Z	8	
Density (calculated)	1.474 Mg/m^3	
Absorption coefficient	0.246 mm^{-1}	
F(000)	1424	
Crystal size	0.80 x 0.70 x 0.20 mm^3	
Theta range for data collection	2.77 to 27.50°.	
Index ranges	-18<=h<=18, -9<=k<=9, -37<=l<=37	
Reflections collected	6643	
Independent reflections	6643 [R(int) = 0.0000]	
Completeness to theta = 27.50°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9524 and 0.8274	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6643 / 1 / 427	
Goodness-of-fit on F^2	1.142	
Final R indices [I>2sigma(I)]	R1 = 0.0481, wR2 = 0.0885	
R indices (all data)	R1 = 0.0630, wR2 = 0.0955	
Absolute structure parameter	0.48(8)	
Extinction coefficient	0.0044(7)	
Largest diff. peak and hole	0.318 and -0.306 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **165**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	8150(1)	2045(1)	4789(1)	17(1)
S(2)	9438(1)	-7079(1)	1138(1)	17(1)
F(1)	7935(1)	2376(2)	3489(1)	30(1)
F(2)	7058(1)	-3334(3)	2939(1)	33(1)
F(3)	9670(1)	-7392(2)	2447(1)	32(1)
F(4)	10587(1)	-1698(3)	2991(1)	33(1)
O(1)	7398(1)	1116(3)	4552(1)	21(1)
O(2)	9800(1)	-206(3)	4438(1)	19(1)
O(3)	10202(1)	-6148(3)	1364(1)	23(1)
O(4)	7819(1)	-4759(3)	1499(1)	22(1)
N(1)	7989(2)	3637(4)	5114(1)	25(1)
N(2)	10782(2)	2819(3)	3975(1)	19(1)
N(3)	10649(2)	4649(4)	3905(1)	25(1)
N(4)	11833(2)	4149(4)	4398(1)	25(1)
N(5)	9585(2)	-8705(4)	823(1)	25(1)
N(6)	6821(2)	-7776(4)	1950(1)	20(1)
N(7)	6932(2)	-9588(4)	2036(1)	26(1)
N(8)	5811(2)	-9096(4)	1504(1)	27(1)
C(1)	8968(2)	2577(4)	4345(1)	17(1)
C(2)	9370(2)	909(4)	4095(1)	17(1)
C(3)	9204(2)	-969(4)	4786(1)	22(1)
C(4)	8782(2)	417(5)	5117(1)	21(1)
C(5)	8136(2)	-541(6)	5458(1)	29(1)
C(6)	10159(2)	1506(4)	3771(1)	20(1)
C(7)	11296(2)	5358(5)	4164(1)	26(1)
C(8)	11480(2)	2563(4)	4272(1)	22(1)
C(9)	8715(2)	-214(4)	3792(1)	17(1)
C(10)	8048(2)	539(4)	3505(1)	19(1)
C(11)	7482(2)	-452(5)	3216(1)	21(1)
C(12)	7609(2)	-2304(4)	3216(1)	21(1)
C(13)	8281(2)	-3145(4)	3470(1)	21(1)

C(14)	8836(2)	-2089(4)	3752(1)	19(1)
C(15)	8639(2)	-7577(4)	1593(1)	17(1)
C(16)	8240(2)	-5893(4)	1840(1)	18(1)
C(17)	8420(2)	-4049(4)	1147(1)	24(1)
C(18)	8793(2)	-5471(5)	808(1)	23(1)
C(19)	9407(2)	-4603(6)	444(2)	35(1)
C(20)	7446(2)	-6467(4)	2162(1)	23(1)
C(21)	6303(2)	-10310(5)	1759(1)	26(1)
C(22)	6161(2)	-7515(5)	1635(1)	25(1)
C(23)	8901(2)	-4797(4)	2148(1)	16(1)
C(24)	9570(2)	-5548(4)	2429(1)	18(1)
C(25)	10145(2)	-4563(5)	2712(1)	22(1)
C(26)	10024(2)	-2710(4)	2714(1)	22(1)
C(27)	9364(2)	-1853(4)	2459(1)	24(1)
C(28)	8802(2)	-2907(4)	2178(1)	20(1)

Table 3. Bond lengths [Å] and angles [°] for **165**.

S(1)-O(1)	1.461(2)
S(1)-N(1)	1.516(3)
S(1)-C(4)	1.782(3)
S(1)-C(1)	1.789(3)
S(2)-O(3)	1.461(2)
S(2)-N(5)	1.514(3)
S(2)-C(18)	1.783(3)
S(2)-C(15)	1.790(3)
F(1)-C(10)	1.362(4)
F(2)-C(12)	1.362(3)
F(3)-C(24)	1.365(4)
F(4)-C(26)	1.366(3)
O(2)-C(2)	1.428(4)
O(2)-C(3)	1.440(4)
O(4)-C(16)	1.427(4)
O(4)-C(17)	1.437(4)
N(2)-C(8)	1.341(4)
N(2)-N(3)	1.375(4)
N(2)-C(6)	1.451(4)
N(3)-C(7)	1.310(5)
N(4)-C(8)	1.325(4)
N(4)-C(7)	1.363(5)
N(6)-C(22)	1.336(4)
N(6)-N(7)	1.365(4)
N(6)-C(20)	1.459(4)
N(7)-C(21)	1.326(5)
N(8)-C(22)	1.325(4)
N(8)-C(21)	1.360(5)
C(1)-C(2)	1.538(4)
C(2)-C(9)	1.534(4)
C(2)-C(6)	1.544(4)
C(3)-C(4)	1.525(5)
C(4)-C(5)	1.532(4)
C(9)-C(10)	1.393(4)

C(9)-C(14)	1.395(4)
C(10)-C(11)	1.379(4)
C(11)-C(12)	1.375(5)
C(12)-C(13)	1.370(5)
C(13)-C(14)	1.385(4)
C(15)-C(16)	1.542(4)
C(16)-C(23)	1.536(4)
C(16)-C(20)	1.541(4)
C(17)-C(18)	1.529(5)
C(18)-C(19)	1.520(5)
C(23)-C(24)	1.384(4)
C(23)-C(28)	1.400(4)
C(24)-C(25)	1.374(4)
C(25)-C(26)	1.374(5)
C(26)-C(27)	1.364(5)
C(27)-C(28)	1.389(4)

O(1)-S(1)-N(1)	122.02(14)
O(1)-S(1)-C(4)	108.73(15)
N(1)-S(1)-C(4)	105.85(17)
O(1)-S(1)-C(1)	105.83(13)
N(1)-S(1)-C(1)	111.92(15)
C(4)-S(1)-C(1)	100.35(14)
O(3)-S(2)-N(5)	121.87(14)
O(3)-S(2)-C(18)	109.17(14)
N(5)-S(2)-C(18)	106.37(17)
O(3)-S(2)-C(15)	105.49(13)
N(5)-S(2)-C(15)	111.53(15)
C(18)-S(2)-C(15)	100.32(14)
C(2)-O(2)-C(3)	115.9(2)
C(16)-O(4)-C(17)	115.7(2)
C(8)-N(2)-N(3)	109.8(2)
C(8)-N(2)-C(6)	129.8(3)
N(3)-N(2)-C(6)	120.3(2)
C(7)-N(3)-N(2)	101.8(3)
C(8)-N(4)-C(7)	102.4(3)

C(22)-N(6)-N(7)	110.4(3)
C(22)-N(6)-C(20)	129.7(3)
N(7)-N(6)-C(20)	119.7(2)
C(21)-N(7)-N(6)	101.6(3)
C(22)-N(8)-C(21)	102.7(3)
C(2)-C(1)-S(1)	114.4(2)
O(2)-C(2)-C(9)	110.9(2)
O(2)-C(2)-C(1)	107.7(2)
C(9)-C(2)-C(1)	117.2(2)
O(2)-C(2)-C(6)	104.5(2)
C(9)-C(2)-C(6)	106.0(2)
C(1)-C(2)-C(6)	109.8(2)
O(2)-C(3)-C(4)	114.6(2)
C(3)-C(4)-C(5)	109.9(3)
C(3)-C(4)-S(1)	109.1(2)
C(5)-C(4)-S(1)	109.3(2)
N(2)-C(6)-C(2)	114.4(2)
N(3)-C(7)-N(4)	115.8(3)
N(4)-C(8)-N(2)	110.2(3)
C(10)-C(9)-C(14)	115.7(3)
C(10)-C(9)-C(2)	123.9(3)
C(14)-C(9)-C(2)	120.0(3)
F(1)-C(10)-C(11)	115.6(3)
F(1)-C(10)-C(9)	119.9(3)
C(11)-C(10)-C(9)	124.5(3)
C(12)-C(11)-C(10)	116.2(3)
F(2)-C(12)-C(13)	118.9(3)
F(2)-C(12)-C(11)	118.1(3)
C(13)-C(12)-C(11)	123.0(3)
C(12)-C(13)-C(14)	118.5(3)
C(13)-C(14)-C(9)	121.9(3)
C(16)-C(15)-S(2)	114.7(2)
O(4)-C(16)-C(23)	111.0(2)
O(4)-C(16)-C(20)	104.4(2)
C(23)-C(16)-C(20)	105.7(2)
O(4)-C(16)-C(15)	108.4(2)

C(23)-C(16)-C(15)	116.8(2)
C(20)-C(16)-C(15)	109.9(2)
O(4)-C(17)-C(18)	114.6(3)
C(19)-C(18)-C(17)	111.2(3)
C(19)-C(18)-S(2)	109.5(2)
C(17)-C(18)-S(2)	107.7(2)
N(6)-C(20)-C(16)	113.6(2)
N(7)-C(21)-N(8)	115.2(3)
N(8)-C(22)-N(6)	110.1(3)
C(24)-C(23)-C(28)	115.6(3)
C(24)-C(23)-C(16)	124.7(3)
C(28)-C(23)-C(16)	119.5(3)
F(3)-C(24)-C(25)	115.8(3)
F(3)-C(24)-C(23)	119.6(3)
C(25)-C(24)-C(23)	124.5(3)
C(24)-C(25)-C(26)	116.5(3)
C(27)-C(26)-F(4)	119.1(3)
C(27)-C(26)-C(25)	123.1(3)
F(4)-C(26)-C(25)	117.8(3)
C(26)-C(27)-C(28)	118.1(3)
C(27)-C(28)-C(23)	122.0(3)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **165**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	16(1)	19(1)	17(1)	0(1)	-1(1)	0(1)
S(2)	16(1)	20(1)	16(1)	0(1)	-2(1)	1(1)
F(1)	42(1)	13(1)	34(1)	0(1)	-16(1)	6(1)
F(2)	32(1)	35(1)	32(1)	-14(1)	-1(1)	-16(1)
F(3)	43(1)	15(1)	38(1)	-2(1)	-18(1)	5(1)
F(4)	31(1)	36(1)	30(1)	-12(1)	-1(1)	-16(1)
O(1)	16(1)	24(1)	24(1)	0(1)	-3(1)	-2(1)
O(2)	18(1)	23(1)	17(1)	3(1)	-3(1)	2(1)
O(3)	18(1)	21(1)	29(1)	4(1)	-4(1)	-3(1)
O(4)	18(1)	27(1)	22(1)	0(1)	-3(1)	4(1)
N(1)	26(1)	28(2)	21(1)	-3(1)	1(1)	3(1)
N(2)	17(1)	17(1)	23(1)	-1(1)	1(1)	-3(1)
N(3)	26(1)	21(1)	28(2)	5(1)	-4(1)	-6(1)
N(4)	19(1)	29(2)	28(1)	-6(1)	-2(1)	-1(1)
N(5)	26(1)	27(2)	21(1)	-5(1)	0(1)	7(1)
N(6)	18(1)	22(1)	21(1)	-4(1)	0(1)	-4(1)
N(7)	25(1)	25(1)	29(2)	0(1)	-2(1)	-5(1)
N(8)	21(1)	27(2)	34(2)	-7(1)	-3(1)	-4(1)
C(1)	17(1)	17(2)	19(1)	0(1)	2(1)	-2(1)
C(2)	19(1)	15(2)	17(1)	0(1)	-2(1)	2(1)
C(3)	25(1)	21(2)	19(1)	6(1)	-2(1)	2(1)
C(4)	22(1)	24(2)	17(2)	7(2)	-4(1)	0(1)
C(5)	29(2)	38(2)	20(2)	8(2)	2(1)	-5(1)
C(6)	22(2)	19(2)	19(1)	-5(1)	-1(1)	-3(1)
C(7)	23(2)	23(2)	30(2)	-1(2)	-2(1)	-5(1)
C(8)	15(1)	26(2)	25(2)	-4(1)	-1(1)	4(1)
C(9)	17(1)	15(2)	17(2)	2(1)	2(1)	-1(1)
C(10)	22(1)	13(2)	21(2)	-3(2)	0(1)	0(1)
C(11)	17(1)	26(2)	20(2)	-2(2)	-1(1)	2(1)
C(12)	21(1)	25(2)	18(1)	-9(1)	3(1)	-8(1)
C(13)	29(2)	14(2)	20(2)	-3(1)	7(1)	-2(1)

C(14)	22(1)	16(2)	20(1)	-1(1)	1(1)	1(1)
C(15)	18(1)	19(2)	16(1)	0(1)	-2(1)	-5(1)
C(16)	15(1)	20(2)	19(2)	1(1)	-2(1)	-1(1)
C(17)	27(2)	20(2)	24(2)	5(1)	-6(1)	5(1)
C(18)	23(1)	27(2)	18(2)	1(2)	-7(1)	3(1)
C(19)	43(2)	38(2)	25(2)	14(2)	1(1)	9(2)
C(20)	20(1)	26(2)	24(2)	-9(1)	2(1)	-6(1)
C(21)	26(2)	21(2)	31(2)	-3(2)	4(1)	-5(1)
C(22)	17(1)	27(2)	30(2)	-4(1)	-1(1)	2(1)
C(23)	20(1)	14(2)	14(2)	0(1)	-1(1)	-1(1)
C(24)	21(1)	12(2)	21(2)	1(2)	0(1)	2(1)
C(25)	18(1)	30(2)	17(2)	-2(2)	-1(1)	-2(1)
C(26)	22(1)	24(2)	20(1)	-7(1)	4(1)	-11(1)
C(27)	32(2)	13(2)	27(2)	-4(1)	7(1)	-3(1)
C(28)	24(1)	19(2)	18(1)	3(1)	1(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **165**.

	x	y	z	U(eq)
H(1A)	8670	3370	4111	21
H(1B)	9476	3276	4487	21
H(3A)	9555	-1865	4971	26
H(3B)	8703	-1633	4627	26
H(4)	9279	1046	5294	25
H(5A)	7647	-1151	5285	44
H(5B)	7868	357	5670	44
H(5C)	8481	-1443	5638	44
H(6A)	10513	415	3680	24
H(6B)	9893	2035	3485	24
H(7)	11385	6634	4187	31
H(8)	11692	1412	4376	26
H(11)	7030	113	3027	25
H(13)	8363	-4425	3453	25
H(14)	9314	-2657	3923	23
H(15A)	8127	-8291	1460	21
H(15B)	8947	-8350	1827	21
H(17A)	8943	-3442	1302	28
H(17B)	8085	-3113	967	28
H(18)	8271	-6103	652	27
H(19A)	9078	-3606	292	53
H(19B)	9578	-5516	211	53
H(19C)	9961	-4128	593	53
H(20A)	7705	-7003	2449	28
H(20B)	7095	-5370	2252	28
H(21)	6204	-11584	1740	31
H(22)	5970	-6363	1521	29
H(25)	10603	-5134	2896	26
H(27)	9292	-571	2474	29
H(28)	8336	-2329	2000	24

H(1N)	7750(30)	4370(60)	4966(17)	42(13)
H(2N)	9890(30)	-9540(60)	988(15)	39(11)

Table 6. Hydrogen bonds for **165** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	(DHA)
N(1)-H(1N)...N(4)#1	0.77(5)	2.37(5)	3.119(4)	163(5)
N(5)-H(2N)...N(8)#2	0.89(4)	2.24(4)	3.106(4)	163(4)

Symmetry transformations used to generate equivalent atoms:

#1 x-1/2,-y+1,z #2 x+1/2,-y-2,z

Chapter 7

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